

Comparative Aspects of Triptans in Treating Migraine

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Triptans, beginning with sumatriptan, have revolutionized the treatment of migraine. New triptans in several formulations will soon become available in the United States. Although the similarities of these 5-hydroxytryptamine (5-HT)_{1B/1D} receptor agonists outweigh their differences, important differences in pharmacokinetics and clinical responses do exist.

Subcutaneous sumatriptan has the most rapid onset of action and greatest efficacy but the most adverse effects. Intranasal sumatriptan also has rapid onset of action, but at 2 hours its efficacy is comparable to that of oral zolmitriptan. Of the oral triptans, rizatriptan seems to have the greatest early efficacy. Both rizatriptan and zolmitriptan are now available as rapidly dissolving wafers. Almotriptan, the newest of the triptans, has a response rate similar to that of oral sumatriptan and may produce fewer adverse effects. Naratriptan and frovatriptan, with their slow onset, high tolerability, and long half-lives, may have a role in aborting prolonged migraine attacks and in headache prevention. Eletriptan* at higher doses (80 mg) has a response rate approaching that of rizatriptan but may be limited by potential side effects.*

The many triptans available offer the opportunity to individualize migraine treatment, depending on the patient's attack characteristics, tolerance, and preferences.

INTRODUCTION

The class of triptans has truly revolutionized the treatment of migraine. Nearly 57% of migraineurs report their headaches cause moderate to severe disability (1). This disability can often be prevented by the prudent use of the 5-hydroxytryptamine (5-HT)_{1B/1D} receptor agonists. The number of new triptan medications that are now available or will be available is a tribute to the efficacy of sumatriptan as the first of this class. Sumatriptan has been followed by zolmitriptan, naratriptan, rizatriptan,

and almotriptan. Eletriptan* and frovatriptan* will likely become available in the United States soon.

Although the similarities of the triptans are far more numerous than their differences, the differences may suggest the use of one product over another. It is currently impossible to predict with any degree of certainty which is the *best* triptan for any one patient—a patient may respond to one triptan when another is ineffective (2). The different

* Use not FDA approved.

properties of the triptans make it possible for the clinician to individualize treatment according to migraine characteristics and patient needs. **Table I** lists the available triptans with typical dose recommendations. **Table II** summarizes the comparative characteristics of the available triptans.

KEY POINT

Differences in pharmacokinetics and clinical effects may suggest the selection of one triptan over another; however, it is impossible to predict with any degree of certainty which is the best triptan for a patient.

EFFICACY OF AVAILABLE TRIPTANS

Sumatriptan

Sumatriptan was introduced in the United States in 1992 as a subcutaneous (SQ) injection. As the first triptan to become available, it is also the most studied. Response to SQ sumatriptan is extremely rapid, with some patients reporting a reduction in pain within 10 minutes after a dose is administered (3). In placebo-controlled trials, 70% to 73% of patients given 6 mg of SQ sumatriptan reported pain relief within 1 hour. In its intranasal formulation, 20 mg of sumatriptan relieved pain within 2 hours in 55% to 64% of patients (4) and has been found to be more effective than dihydroergotamine nasal spray in relieving pain and migraine-associated symptoms (5). Between 50% and 61% of patients reported pain relief at 2 hours with 50 mg oral sumatriptan (6) (**Figure**).

The widespread use of sumatriptan has given physicians a sense of confidence with this medication. It has been used to treat over 300 million migraine attacks worldwide. The rapidity and effectiveness of the SQ preparation make it unique within the class and the best form of treatment for patients with severe migraine accompanied by nausea and vomiting. Patients who awaken with migraine, or have a rapid-onset migraine, or have neglected to take their migraine-abortive medica-

tion early enough find the SQ preparation especially valuable.

The 3 forms of administration can be an advantage for patients. For example, if a headache recurs after initial treatment with the SQ form, the patient can follow up with either the oral or intranasal form of sumatriptan.

Zolmitriptan

Zolmitriptan was the second triptan approved for use in the United States. At a dose of 2.5 mg, zolmitriptan relieves pain in 62% to 65% of patients within 2 hours after administration (7); response rates are similar for the 2.5-mg and 5-mg doses (8). Studies suggest that oral zolmitriptan has slightly higher efficacy at 2 hours than oral sumatriptan.

Zolmitriptan has recently become available as a rapidly dissolving wafer, which allows patients to take the drug without water, a convenience not offered by the standard tablet form. Its efficacy in this formulation is similar to the tablet form (7). Zolmitriptan also will soon become available in the United States as a nasal spray.

Rizatriptan

At a dose of 10 mg, rizatriptan has a high response rate for an oral triptan. It relieves pain within 2 hours in 67% to 77% of patients (9). Some patients experience pain relief as soon as 30 minutes after dosing (10,11). Rizatriptan was the first triptan offered in a rapidly dissolving wafer formulation. The early response of this drug (30 minutes, 1 hour, and 2 hours) is greater than with other oral or wafer formulations of triptans currently available. This early response may be related to the short maximal plasma concentration (T_{max}) time (1 hour) during a migraine attack compared with the other oral triptans (≥ 2 hours).

Naratriptan

Clinical trials of naratriptan differ from those of other triptans in that the primary efficacy endpoint was pain relief at 4 hours rather than 2 hours. Among patients taking 2.5 mg of naratriptan, between 60% and 66% reported pain relief at 4 hours (12). The data suggest that ~40% of patients

TABLE I.

AVAILABLE TRIPTANS WITH TYPICAL DOSE RECOMMENDATIONS

Name	Formulation	Available Dose	Package Size	Adult Start Dose	Repeat Time	Maximum Dose in 4 Hours
Sumatriptan succinate (Imitrex®)	SQ	6 mg	2	6 mg	1 h	12 mg
	NS	5 mg, 20 mg	6	20 mg	2 h	40 mg
	Tablet	25 mg, 50 mg, 100 mg	9	50 mg	2 h	200 mg
Zolmitriptan (Zomig™)	Tablet	2.5 mg, 5 mg	3, 6	2.5 mg	2 h	10 mg
	Wafer	2.5 mg (5 mg will be available soon)	6	2.5 mg	2 h	10 mg
Naratriptan HCl (Amerge™)	Tablet	1 mg, 2.5 mg	9	2.5 mg	4 h	5 mg
Rizatriptan benzoate (Maxalt®), (Maxalt-MLT™)	Tablet	5 mg, 10 mg	6	10 mg	2 h	30 mg
	Wafer	5 mg, 10 mg	6	10 mg	2 h	30 mg
Almotriptan malate (Axert®)	Tablet	6.25 mg, 12.5 mg	6	12.5 mg	2 h	25 mg

SQ = subcutaneous; NS = nasal spray.

treated with naratriptan experience pain relief at 2 hours, although these data were not reported in pivotal clinical trials (13). Package insert (PI) information suggests that naratriptan is better tolerated than other available triptans.

The relatively slow onset of action and lower efficacy of naratriptan may be disadvantages, but its longer half-life may offer an advantage. Patients who respond to naratriptan seem to have a lower recurrence rate than those migraineurs who respond to the faster-acting triptans; therefore, it may be useful in longer-duration migraine and to break cycles of status migrainosus. Given prophylactically, naratriptan also has been shown to reduce the occurrence of menstrually associated migraine. As mixing triptans within a 24-hour period is considered a contraindication, the use of naratriptan in this situation limits the use of other faster-acting and more effective triptans in the breakthrough migraines that occur in 50% of patients.

Almotriptan

Almotriptan is the newest of the triptans to be approved for use in the United States. PI data suggest that the effectiveness of oral almotriptan is similar to that of oral sumatriptan. The recurrence

rate of migraine in 18% to 27% of patients across controlled clinical trials compares favorably with published reports of other triptans. The incidence of adverse events (AEs) is generally similar to that of placebo. Comparing PI information of the rapidly-acting oral triptans, the lower rates of fatigue and chest discomfort with almotriptan use may be important.

Eletriptan and Frovatriptan

Eletriptan has been pending FDA approval for some time now. Apparently there is a concern of possible interaction with other compounds that are metabolized by cytochrome P-450. The 2-hour response rate at the 40-mg dose seems to be in the 64% to 68% range; this rate is slightly higher with the 80-mg dose (14). Although eletriptan is generally well tolerated, a high percentage of patients (35% with 40 mg and 51% with 80 mg) report some annoying AEs (15).

The rate of symptoms referable to the chest, shoulder, throat, or neck was high—7%—for both 40 mg and 80 mg of eletriptan.

Frovatriptan has pharmacokinetic properties more similar to naratriptan than to the other triptans with a T_{max} of ~3 hours and a half-life 3 times that

TABLE II.

COMPARISON OF TRIPTAN CHARACTERISTICS

- Speed
sumatriptan SQ>sumatriptan nasal spray=rizatriptan tablet/wafer>zolmitriptan >sumatriptan oral=almotriptan >naratriptan
- Early effectiveness (1 and 2 hours)
sumatriptan SQ>rizatriptan tablet/wafer>sumatriptan nasal spray=zolmitriptan >sumatriptan oral=almotriptan >naratriptan
- Tolerability
naratriptan=almotriptan>sumatriptan oral=zolmitriptan=rizatriptan>sumatriptan nasal spray>sumatriptan SQ
- Recurrence
naratriptan=almotriptan<zolmitriptan=rizatriptan= sumatriptan SQ, oral, nasal spray
- Formulations
sumatriptan>rizatriptan=zolmitriptan>naratriptan=almotriptan

SQ = subcutaneous.

KEY POINT

Response to SQ sumatriptan is extremely rapid with pain reduction reported in some patients within 10 minutes after a dose is administered. Oral rizatriptan has a high response rate of pain relief within 2 hours after dosing, and some patients have experienced pain relief within 30 minutes.

of naratriptan at 24 hours. The onset of action is slow while the recurrence rate of headache is low at 9% to 14%. The pain relief efficacy rate of frovatriptan at 2.5 mg is also similar to that of naratriptan, which is ~40% at 2 hours and 60% at 4 hours (16,17). The extremely long half-life of frovatriptan may make it valuable in aborting long attacks or in treating rebound or transformed migraine.

COMPARISON OF TRIPTAN EFFICACY

In head-to-head comparative trials, the triptans, except for naratriptan and frovatriptan, have fairly comparable efficacy (Table III). In an early study comparing the efficacy and safety of 5 mg of zolmitriptan with 100 mg of sumatriptan, no significant difference in the percentage of patients reporting

pain relief at 2 hours emerged (18). In a recently published study involving nearly 1500 migraineurs, the difference in response rate between patients treated with 2.5 mg of zolmitriptan and those given 50 mg of sumatriptan was statistically significant at both 2 hours and 4 hours (19); 67% of patients treated with 2.5 mg of zolmitriptan reported pain relief at 2 hours compared with 64% of those given 50 mg of sumatriptan ($P = .017$). At 4 hours, 83% of patients given 2.5 mg of zolmitriptan reported pain relief compared with 81% of those given 50 mg of sumatriptan ($P = .039$).

A comparative trial demonstrated no difference between 12.5 mg of almotriptan (58%) and 50 mg of sumatriptan (57%) in the 2-hour response rate and symptom relief (20). Likewise, pain relief was similar at 0.5 and 1 hour as was the rate of recurrence and the use of rescue medicine. The 2-hour pain-free response rate of sumatriptan (25%) was significantly better than almotriptan (18%); however, the almotriptan group reported significantly fewer drug-related AEs (9.1%) compared with sumatriptan (15.5%), with the greatest differences being in chest pain and nausea.

In a comparative trial of 2.5 mg of naratriptan and 10 mg of rizatriptan, naratriptan was considerably less effective than rizatriptan. At the 2-hour endpoint, 48% of patients treated with naratriptan reported pain relief compared with 69% treated with rizatriptan; this difference was statistically signifi-

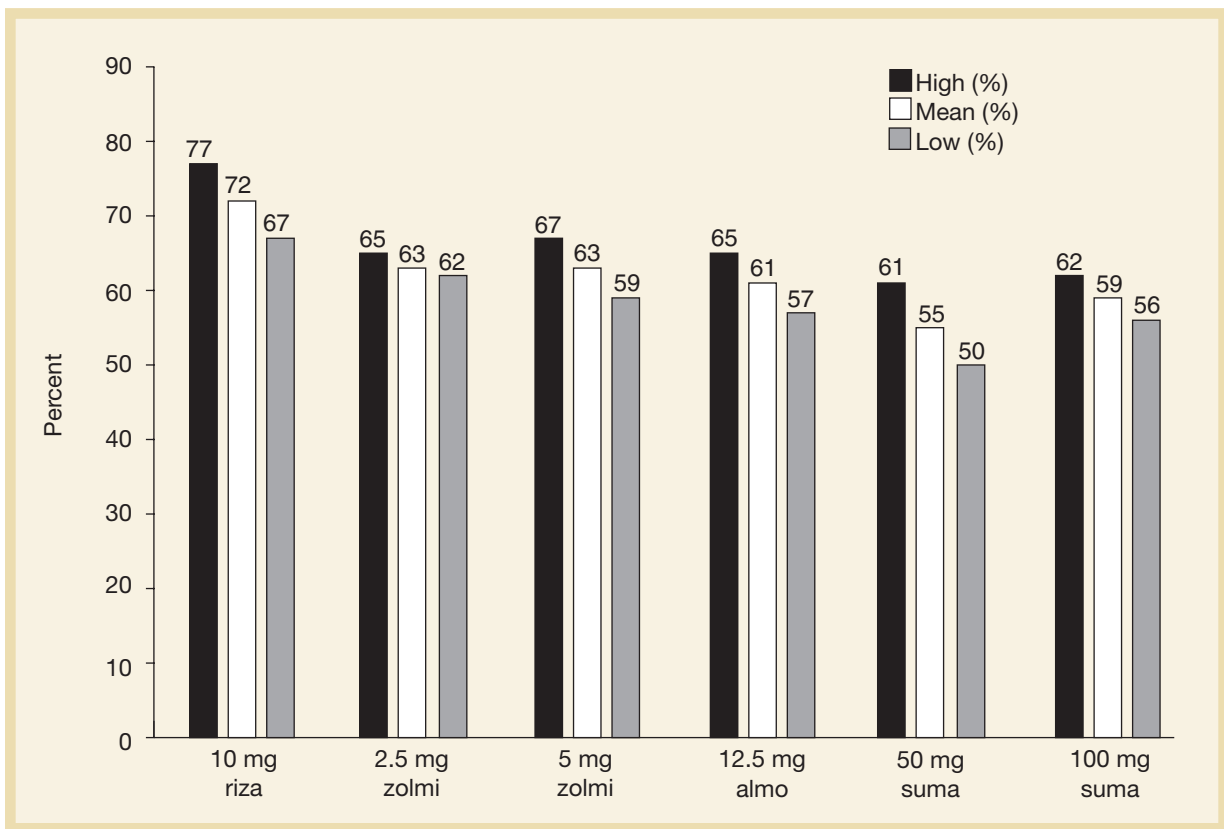


Figure. Two-hour pain relief response was not primary endpoint for naratriptan. The package insert indicated a 2-hour response probability of 48% on a Kaplan-Meier plot. riza = rizatriptan; zolmi = zolmitriptan; almo = almotriptan; suma = sumatriptan.

cant ($P < .001$). The 2-hour pain-free response was twice as great with rizatriptan versus naratriptan (45% vs 21%), and although naratriptan has a longer half-life, the sustained pain-free response was greater with rizatriptan (29% vs 17%) (21). In studies comparing 10 mg of rizatriptan with zolmitriptan and sumatriptan, a slightly greater percentage of patients taking rizatriptan reported pain relief within 2 hours compared with those taking 2.5 mg of zolmitriptan (71% versus 67%) (22); 50 mg of sumatriptan (72% versus 68%) (23); or 100 mg of sumatriptan (67% versus 62%) (24), although the difference in response rates was not statistically significant.

Patient Preferences

Patients want quick relief of their head pain (25). They consider “quick” to be 1 hour or less. In a survey of migraineurs, more than 90% of these patients wanted a migraine medication that could satisfactorily relieve pain within 1 hour (25).

Statistically significant differences in the percentage of patients reporting pain relief at 1 hour have been documented (22–24). In most of the studies in which 10 mg of rizatriptan was compared with other triptans, rizatriptan was more effective in relieving pain within 1 hour ($P < .05$, 10 mg rizatriptan versus 100 mg sumatriptan, 2.5 mg naratriptan, and 2.5 mg zolmitriptan). A recent review by Marcus (26) emphasizes the importance of the early response and suggests that preference for rizatriptan among the oral triptans relates to the speed of relief (Table IV). Data on the percentage of patients who were completely pain free at 2 hours show similar differences among the triptans.

The recurrence rate among the triptans may differ. In most studies “recurrence” is defined as the return of a moderate or severe headache within 24 hours after the pain has decreased from moderate or severe to mild or none. Sumatriptan, zolmitriptan, rizatriptan, and eletriptan have similar

TABLE III.

HEADACHE RESPONSE AND THERAPEUTIC GAIN FOR SELECTED TRIPTANS AT 2 HOURS

	Headache Response (%)	Therapeutic Gain for Response (%)*
Almotriptan (25 mg)	57–68	19–27
Eletriptan (40 mg)	54–65	22–41
Eletriptan (80 mg)	68–77	30–53
Frovatriptan (2.5 mg)	40	16
Naratriptan (2.5 mg)	48 (45–51)	21 (18–24)
Rizatriptan (10 mg)	73 (69–73)	34 (30–38)
Sumatriptan (20 mg NS)	60–86	28–55
Sumatriptan (50 mg)	56 (51–61)	33 (29–36)
Sumatriptan (6 mg SC)	80–85	51
Zolmitriptan (2.5 mg)	64 (59–69)	34 (27–41)

*Therapeutic gain = % treatment response rate–% placebo response rate. NS = nasal spray; SC = subcutaneous. Reprinted with permission from Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache and Other Head Pain*. 7th ed. Oxford, England: Oxford University Press; 2001:168.

recurrence rates of ~30% to 40%. Of the more rapidly-acting triptans, the recurrence rate may be lower for almotriptan at 18% to 27%. Naratriptan and frovatriptan have a lower recurrence rate but also a lower rate of pain relief; the faster-acting agents, led by rizatriptan, have a higher percentage of patients with a sustained 24-hour, pain-free response rate (27).

COMPARISON OF ADVERSE EFFECTS OF TRIPTANS

Triptan AEs can be divided into the annoying ones and the serious ones. The annoying AEs tend to be similar with all the triptans and include malaise, fatigue, tingling, paresthesias, dizziness, flushing, sensation of heat, and a feeling of heaviness or pressure in the neck or chest. SQ sumatriptan has the highest rate (42%) of associated atypical sensations (eg, warmth, burning, and tingling) among the triptans. In premarketing studies, up to 59% of patients may also experience injection-site reactions (3). The incidence of AEs may be related to the speed of onset of action. SQ sumatriptan, for example, has an extremely rapid onset of action, but compared with oral sumatriptan causes a greater number of AEs (28). In contrast, naratriptan and frovatriptan, which have a slower onset of action, tend to cause fewer AEs (29).

PI information suggests little difference

KEY POINT

Adverse effects of the triptans can be divided into the annoying ones, such as malaise, dizziness and nausea, and the serious ones, which relate to their vasoconstricting properties. Cardiovascular risk factors such as hypertension, smoking, obesity, diabetes, and a family history of vascular disease should be evaluated before prescribing a triptan.

among the oral formulations regarding side-effect profile. Based on premarketing studies, zolmitriptan has the highest percentage of atypical sensations, experienced at 18% with the 5-mg dose; rizatriptan at 5 mg and 10 mg, naratriptan at 1 mg and 2.5 mg, and sumatriptan at 25 mg and 50 mg are on the order of 4% to 6%. Fatigue, dizziness, and somnolence—all ~10% or less with rizatriptan and zolmitriptan—occur more frequently than with sumatriptan and naratriptan and may be due to the greater lipophilicity seen with rizatriptan and zolmitriptan, resulting in greater central nervous system penetration. The PI reports that the AE profile of almotriptan is similar to that of placebo,

TABLE IV.

TRIPTAN EFFICACY AND TIME TO PEAK BLOOD CONCENTRATION (T_{MAX})*

Triptan	T_{max} (h)	Pain Relief, %			Pain Free, %	
		30 Minutes	1 Hour	2 Hours	1 Hour	2 Hours
Sumatriptan succinate, 100 mg	2.5	NA	20 (12)	55 (24)	6 (2)	23 (6)
Zolmitriptan, 5 mg	2–3	12 (5)	40 (22)	62 (35)	NA	39 (1)
Rizatriptan benzoate, 10 mg	1–1.5	22 (11)	45 (21)	74 (28)	13 (3)	42 (10)
Naratriptan hydrochloride, 2.5 mg	3–4	7 (5)	20 (15)	40 (30)	NA	NA
Eletriptan, 40 mg	2.8	NA	38 (12)	65 (24)	8 (2)	29 (8)
Eletriptan, 80 mg	2.8	NA	41 (12)	77 (24)	17 (2)	37 (8)
Frovatriptan, 2.5 mg	2–3	NA	NA	40 (24)	NA	NA
Almotriptan, 12.5 mg [†]	2.6	13	34	58	5	18

*Placebo responses are shown in parentheses. NA indicates data not available.

[†]Almotriptan was compared with sumatriptan, not placebo.

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with only nausea, dry mouth, and paresthesias occurring slightly more frequently.

Pain or pressure associated with the triptans may be site specific, such as the chest, neck, or jaw, or may be experienced as a general widespread sensation. In premarketing trials, chest pain has been reported at 3% for zolmitriptan with the 2.5-mg dose and 4% with the 5-mg dose; for rizatriptan <2% with the 5-mg dose and 3% with the 10-mg dose; 4% with 2.5 mg of naratriptan; and for sumatriptan 1%, 2%, and 2%, respectively, with the 25-mg, 50-mg, and 100-mg doses. Of subjects treated with SQ sumatriptan, 3% complained of chest tightness with 2% having chest pressure. The incidence of chest pain among subjects treated with almotriptan is <1%. Like chest discomfort, neck discomfort is also seen in a small number of patients. Some patients find the taste of the sumatriptan nasal spray disagreeable, which may be lessened by sucking hard candy.

CARDIOVASCULAR CONCERNS

The potentially severe AEs of the triptans relate to their vasoconstricting properties. Vascular events, including deaths, have been noted in patients using triptans. These events have been more frequently noted in postmarketing reports and as such the relevance remains speculative. These reports do not

always clarify the role of the drug in the AE. In most patients who developed cardiac events, various cardiac risk factors were present prior to triptan usage.

In premarketing studies involving >1900 patients, SQ sumatriptan was associated with coronary artery vasospasm in 8 patients that may have occurred during or shortly after its use (3). Six of the 8 patients had electrocardiographic (ECG) changes consistent with transient ischemia but without other symptoms or signs. Four of these patients had various risk factors for coronary artery disease.

In clinical trials, 2 of 6348 patients using oral sumatriptan experienced events consistent with coronary artery constriction but without severe adverse outcomes (6). Of >4000 patients participating in premarketing studies of intranasal sumatriptan, 1 subject experienced an asymptomatic subendocardial infarct, possibly due to vasoconstriction (4). In premarketing studies involving >2500 patients, zolmitriptan produced no severe cardiac events (7); of ~3500 naratriptan-treated patients, 4 had ischemic ECG changes consistent with vasospasm (12); and of 3700 patients studied, 1 10-mg rizatriptan-treated patient had chest pain with possible ischemic ECG changes (9). Of >3800 almotriptan-treated patients, 1 had an abnormal ECG 48 hours after a single dose, which was believed due to myocardial ischemia (30).

METABOLIC DIFFERENCES OF TRIPTANS

Differences exist in triptan metabolism and these differences may allow for the favorable use of one triptan over another. Other than naratriptan, triptans are metabolized by monoamine oxidase (MAO) A and the use of MAO inhibitors would be expected to elevate plasma levels. Therefore, rizatriptan, sumatriptan, and zolmitriptan should not be prescribed for patients taking MAO inhibitors or within 2 weeks of discontinuing use of an MAO inhibitor. Almotriptan is partially metabolized by MAO, although the PI mentions that dose adjustment is not necessary. Because MAO inhibitors may be used by patients with depression, a disorder that has significant comorbid association with migraine, this may be of clinical importance.

Hepatic and renal clearance also must be considered. Except for sumatriptan, which is largely metabolized to an inactive substance, the metabolism of the other triptans is altered in renal

KEY POINT

MAO inhibitors metabolize rizatriptan, sumatriptan, and zolmitriptan; therefore, these triptans should not be prescribed for patients taking MAO inhibitors. Renal and hepatic clearance also must be considered.

impairment, which requires that their dosage be decreased. In patients with severe renal impairment, the clearance rate of zolmitriptan is reduced by 25% (7). In patients with moderate renal impairment, naratriptan has a 50% clearance reduction, with an increase in maximal drug concentration by 40% and an increase in half-life (12). Rizatriptan shows a 44% increase in area under the curve in patients with severe renal impairment with no significant change noted in patients with moderate renal impairment (9). The clearance rate of almotriptan is reduced by 40% in patients with moderate renal impairment and by 65% in patients with severe renal impairment.

Also, except for SQ sumatriptan, with the

other triptans hepatic impairment may increase plasma levels; therefore, for patients with hepatic or renal impairment dosage adjustments must be considered. The PI for oral sumatriptan and naratriptan lists severe hepatic impairment as a contraindication to their use. With naratriptan the PI also lists severe renal impairment (creatinine clearance <15 mL/min) as a contraindication.

Medication interactions may occur with the triptans, although only a few appear to be of clinical relevance. Rizatriptan can interact with propranolol, with a subsequent elevation of rizatriptan levels, and it is recommended that 5 mg be used as the initial dose. Zolmitriptan has a similar interaction with propranolol, but no dose adjustment is recommended in the PI. Other β -blockers do not have this effect on rizatriptan or zolmitriptan levels. Cimetidine may interfere with the metabolic breakdown of zolmitriptan with changes in its serum level and half-life. In the presence of cimetidine, a smaller dose of zolmitriptan should be used.

SUMMARY

A comparison of the available triptans shows more similarities than differences. They all have proven efficacy in migraine treatment. Differences in their pharmacokinetics and clinical effects may suggest the selection of one triptan over another, but for any single patient it is impossible to predetermine which will be most effective. Likewise the side effects noted appear in large degree to be a class effect as opposed to an individual difference in chemical structure or property. Differences do occur and may necessitate a change from one triptan to another. The favorable side-effect profile of some of the triptans compared with others in its class also may be of importance in individual selection.

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Dialogue Box

ADVISORY BOARD

What is the mechanism of action of the triptans?

ADELMAN

Triptans are basically a designer group of drugs that fool the brain into thinking it's receiving serotonin. The serotonin receptors they act on are primarily the 5-HT_{1B/1D} receptors—these are not necessarily responsible for starting a headache but are important in stopping one. The 5-HT_{1B} receptors are located primarily on blood vessels and cause vasoconstriction; the 5-HT_{1D} receptors, which are responsible for migraine relief, are located at the trigeminal pathway of the peripheral nerve ganglion in the brain stem. The current emphasis is to develop triptans that act on the 5-HT_{1D} receptor rather than the 5-HT_{1B} because of the fear of vasoconstriction. 5-HT_{1F} receptors are also being looked at since they do not appear to cause vasoconstriction and may have a role in stopping migraine attacks.

ADVISORY BOARD

Are there 1B receptors present on the coronary arteries and are they responsible for the coronary vasoconstriction seen in some patients?

ADELMAN

Yes, 1B receptors are among the vasoconstrictive receptors located on coronary vessels. As a class, the triptans appear to be far more active on meningeal vessels than on coronary vessels. The vasoconstriction seen in the meningeal vessels is 10 times as great as that seen in the coronary vessels.

ADVISORY BOARD

Chest pain or pressure is a fairly common side effect of the triptans. What percentage is related to subendocardial ischemia?

ADELMAN

No one knows the exact percentage; based on electrocardiography and coronary angiography studies, the majority of cases are believed to be noncardiac in origin. We do know there are 5-HT serotonin receptors in the esophagus, and it is likely that these cases are due to esophageal changes. Triptans are contraindicated in patients with ischemic heart disease, however.

ADVISORY BOARD

Is the efficacy of the triptans dependent on the stage of the migraine at which they are used?

ADELMAN

Yes, definitely. Although the duration of a headache prior to the use of a triptan does not appear to make much of a difference, the severity of the headache when a triptan is taken certainly does. For example, if you treat a migraine that's mild, the success rate typically is 70% to 85%. When the migraine is only moderately severe, you're going to get the efficacy typically reported. When you treat a migraine that is severe, you're going to get numbers lower than those quoted in my article.

ADVISORY BOARD

Is it still believed that triptans may not be effective in the very early phases of migraine and that other abortive measures, such as non-steroidal anti-inflammatory drugs (NSAIDs), may be preferable?

ADELMAN

I certainly think so. Surprisingly when the sumatriptan injectable first came out, a study in which it was used during the prodromal or aura stage found that it failed to prevent the headache. As a result, I give 10 mg of metoclopramide plus a



Dialogue Box

large dose of an NSAID to migraine patients in the prodromal stage who feel there's a 50% chance of getting the headache. This accomplishes 3 things: (1) the likelihood of the headache phase of the migraine evolving is reduced by about 50%; (2) the metoclopramide increases the peristaltic movement of the gut so that you get increased absorption of whatever medicine you will take later if needed; and (3) because of the high dose of the NSAID, if a triptan is subsequently taken, the recurrence rate appears to be cut nearly in half. So there is a true advantage to identifying and treating the prodrome.

ADVISORY BOARD

What then do you think of the practice of combining a triptan with a short half-life with one that has a long half-life?

ADELMAN

At this point I'm not comfortable mixing triptans and strongly advise against it. First, this practice is contraindicated by the PI, which states clearly that you should not mix triptans within 24 hours. Second, it is still unknown whether the coronary vasoconstrictive effects of different triptans are additive. In the event of a recurrence, I favor repeating the dose since we know it's safe and that the response to a repeat dose is about 80% with any of the rapidly acting triptans. In other words, although the initial response may be 60% to 70%, when there's a recurrence of the migraine and you repeat the same triptan, the rate of stopping the migraine is about 80%. As a result, for many patients there may be no need for following up with a long-acting triptan, particularly if an NSAID was given during the prodrome.

ADVISORY BOARD

On average, how many doses does the typical migraine patient require?

ADELMAN

That's a good question. If you look at the PI for all of the products, it's stated that the average attack requires 1.4 to 1.5 oral triptan doses per attack. There are 2 reasons why people will take more than 1 dose: (1) they don't get a response—they take a dose, 2 hours later their headache has gotten worse, so they repeat the dose; and (2) the headache goes away but recurs. When you look at the number of tablets used per attack, it's higher with naratriptan because the patient needs a second tablet more frequently.

ADVISORY BOARD

What qualities define the ideal triptan?

ADELMAN

The ideal triptan would be an agent that acts rapidly with a very short time to T_{max} , has a low incidence of side effects and a low recurrence rate, and is convenient for the patient to take.

ADVISORY BOARD

Does the ideal triptan exist?

ADELMAN

No. Although SQ formulations are the most rapidly acting, the high incidence of side effects, cost, and need for an injection tend to discourage their use. Intranasal formulations have not proved popular, with 9 of 10 patients likely to prefer the oral or SQ formulation. Where nausea is an issue, I find the wafer form of rizatriptan helpful—it dissolves rapidly under the tongue, is fairly fast-acting, and it produces a good early and 2-hour pain-relief response. Triptans with longer half-lives, such as naratriptan and frovatriptan, have lower recurrence rates but are associated with a lower early response rate. I take all of these factors into account when I prescribe, and I also factor in whether there is a



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positive family history of migraine response to a specific triptan.

ADVISORY BOARD

What is the maximum amount of a triptan that can be used over a period of time?

ADELMAN

I recommend a maximum of 8 days of use per month for all of the triptans. I also typically limit the use of a triptan to 2 days per week. For the patient with menstrual migraine, I'm comfortable with her using a triptan, say, 3, 4, or 5 days during menses and then sparingly the rest of the month. As far as per-day use, with oral sumatriptan it's 200 mg/d and with the SQ it's 2 injections per day. For zolmitriptan, naratriptan, and rizatriptan, the maximum 24-hour dose is 10 mg, 5 mg, and 30 mg, respectively.

ADVISORY BOARD

Does a triptan response have diagnostic value in patients with headaches? For example, if a headache responds to a triptan, does that mean it's migraine? Conversely, does a lack of response mean the headache is not a migraine?

ADELMAN

I think that's a potentially dangerous way to look at it. If a patient has an episodic headache of moderate severity with any disability, statistically it's going to be a migraine regardless of its response to a triptan. However, I can tell you there are case reports in the literature of people who have gone into the emergency room and it turns out they have subarachnoid hemorrhages despite demonstrating a triptan response. Tension headaches, particularly in a migraineur, have also been shown to respond to a triptan. On the other hand, I have many patients who clearly in my

mind have migraines but don't respond to triptans. Although we make an assumption that migraine is a condition that is probably serotonin related, there may very well be certain migraine patients in whom serotonin may not be the main neurotransmitter involved.

ADVISORY BOARD

Since the long-acting triptans seem less effective than the short-acting ones, what is their role in the treatment of migraine?

ADELMAN

I generally use a long-acting triptan if the short-acting triptan doesn't work and also for patients with status migrainosus. For a patient who has a prolonged headache, I might give 1 naratriptan tablet (2.5 mg) BID for 2 or 3 days, a half tablet BID for 2 more days, and then a half tablet per day for 2 days in an effort to break the cycle.

ADVISORY BOARD

Which triptan do you favor for managing menstrual migraine?

ADELMAN

All the triptans are effective for managing menstrual migraine—there's no triptan that is uniquely effective during menstruation. Having said that, naratriptan is being touted as a drug for menstrual migraine because of its long half-life. However, the problem with using it for menstrual migraine is what are you going to use for an acute attack that breaks through since naratriptan is less effective than the other triptans? Because you shouldn't mix triptans, its use would preclude your using one of the more rapidly effective triptans, such as rizatriptan, zolmitriptan, or sumatriptan.