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THE TRIPTAN FORMULATIONS

A critical evaluation

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ABSTRACT - The migraine-specific triptans have revolutionized the treatment of migraine and are usually the drugs of choice to treat a migraine attack in progress. Different triptans are available in different strengths and formulations including oral tablets, orally disintegrating tablets, nasal sprays and subcutaneous injections. In Europe, sumatriptan is also available as a suppository. Specific differences among the triptans exist as evidenced by different pharmacological profiles including $T_{½}$, T_{max}, C_{max}, *AUC*, metabolism, drug-drug interaction profiles, amongst other parameters. How or whether these differences translate to clinical efficacy and tolerability differences is not well differentiated. Clinical distinctions among these agents are subtle and proper choice of triptan requires attention to the specific characteristics of each individual patient, knowledge of patient preference, accurate history of the efficacy of previous acute care medications as well as individual features of the drug being considered. Delivery systems may play an important role in the onset of action of triptans. The selection of an acute antimigraine drug for a patient depends upon the stratification of the patient's migraine attack by peak intensity, time to peak intensity, level of associated symptoms such as nausea and vomiting, time to associated symptoms, comorbid diseases, and concomitant treatments that might cause drug-drug interactions. The clinician has in his armamentarium an ever-expanding variety of medications, available in multiple formulations and dosages, with good safety and tolerability profiles. Continued clinical use will yield familiarity with the various triptans, and it should become possible for the interested physician to match individual patient needs with the specific characteristics of a triptan to optimize therapeutic benefit.

KEY WORDS: triptans, migraine treatment, acute treatment.

Formulações dos triptanos: avaliacão crítica

RESUMO - Os triptanos, drogas anti-migranosas específicas, revolucionaram o tratamento da migrânea e são considerados as drogas de escolha para o tratamento da crise migranosa. Diferentes triptanos são disponíveis em diferentes formulações, incluindo comprimidos, tabletes de dispersão oral, *sprays* para administração nasal e injeções subcutâneas. Na Europa, sumatriptan também é disponível como supositório. Diferenças específicas entre os triptanos são evidenciadas por seu diferente perfil farmacológico, incluindo $T_{½}$, T_{max}, C_{max}, AU*C*, metabolismo, perfil de interação entre drogas, entre outros parâmetros. Controvérsias existem sobre se, ou como, essas variáveis traduzem-se em eficácia clínica e tolerabilidade. A distinção clínica entre esses agentes é sutil e a escolha adequada de um triptano requer consideração sobre as características específicas de cada paciente, conhecimento da preferência dos mesmos, obtenção de história acurada sobre a eficácia de medicações previamente utilizadas, assim como consideração sobre as características individuais das diversas drogas. A via posológica parece desempenhar importante papel no modo de ação dos triptanos. A seleção de droga antimigranosa adequada para o tratamento da crise migranosa depende da estratificação do ataque de acordo como a intensidade da dor, tempo para que a máxima intensidade da dor seja atingida, sintomas associados, tempo para que os sintomas associados se manifestem, doenças concomitantes e tratamentos adjuvantes que possam causar interações medicamentosas. O clínico dispõe em seu armamentário uma variedade de medicamentos em constante expansão, em múltiplas formulações e dosagens, seguras e com bom perfil de tolerabilidade. O uso continuado dos triptanos perimitirá familiaridade com essa classe de medicação e possibilitará ao clínico a prescrição de drogas com características específicas para atender as necessidades clínicas de diferentes pacientes, de modo a otimizar o benefício terapêutico.

PALAVRAS-CHAVE: triptanos, migrânea, tratmento agudo.

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The pharmacological treatment of migraine is an important part of the full regimen of good management principles for migraine. Pharmacotherapy is traditionally divided into acute-care and preventive medications. Acute-care treatment (also called abortive treatment) is intended to reverse attacks once they begin, the goal being to reduce and ideally stop the pain, associated symptoms and disability[1].

The migraine-specific triptans have revolutionized the treatment of migraine and are usually the drugs of choice to treat a migraine attack in progress. Their mechanism of action is based on the stimulation of specific serotonin (5-hydroxytryptamine; 5-HT) receptors including peripheral 1_B and central and peripheral 1_D subtypes[2]. This results in reversal of vasodilatation and decrease in neurogenic inflammation, as well as reducing central nociception. New triptans are being released in rapid succession with each one demonstrating some specific pharmacokinetic properties which may be translated into clinical advantages. The aim of this article is to critically review the characteristics of these acute care migraine-specific drugs.

THE TRIPTANS

There are seven triptans available in the first quarter of 2002 in some countries. In order of their clinical development, they are sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan (the latter available in some countries although not yet approved by the FDA) and frovatriptan (Table 1).

SUMATRIPTAN

The first selective 5-$HT_{1B/1D}$ agonist to be synthesized was sumatriptan, as a subcutaneous (SC) injection, then as an oral tablet and more recently as a nasal spray (NS)[3]. It is also available in more than 15 countries as a suppository. Sumatriptan is the most extensively studied agent in the history of migraine therapy. Since its release in Europe in 1991, it is estimated to have been used in over 200 million attacks by close to 10 million patients by 1999[4]. Sumatriptan has brought prompt and effective migraine relief that facilitates resumption of work and most normal daily activities for the majority of patients[5]. Subcutaneous sumatriptan, available as a 6 mg dose in a self injectable pen, has the most favorable pharmacokinetic profile of the triptans (Table 2), with a T*max* of 10 min and a bioavailability of 96%[6]. It also has the highest clinical efficacy, with a 2 hour response rate of 76% and a rapidly attained pain free rate of 48% at 60 minutes after administration[6]. It has an intrapatient consistency in multiple attacks ranging from 89% (2 of 3 attacks) to 73% (3 of 3 attacks)[4]. Recurrence of migraine within 24 hours, after improvement at 2 hours, was reported as 34% to 38% in the first 2 large studies[4].

The injection is the fastest way to stop a rapidly progressing severe migraine or migraine present upon awaken. The subcutaneous form is the most efficient way to medicate someone with migraine and severe nausea; however the injection does produce a larger number of typical triptan adverse events (AE's) than other forms, is inconvenient to use, slightly uncomfortable at the site of injection, and is up to three times the price of most triptan tablets.

The oral tablet has a bioavailability of 14%[6], as shown in Table 2. The minimum effective dose is 25 mg, and the optimum doses range from 50 to 100 mg with no gain in efficacy at the higher doses, but more adverse events when dose is increased[7]. Some more recent studies show added effect of the 100 mg tablet when taken at the mild pain level of a progressing migraine attack[8]. Sumatriptan 50 mg

Table 1. Triptan medications.

Generic	Brand	Formulations	Doses	Maximum daily dose
Sumatriptan	IMITREX	Tablets	25 mg, 50 mg, 100 mg	200 mg
		Nasal spray	5 mg and 20 mg	40 mg
		Subcutaneous injection	6 mg	12 mg
		Suppositories	25 mg	50 mg
Zolmitriptan	ZOMIG	Tablets	2.5 mg, 5mg	10 mg
	ZOMIG-ZMT	Orally disintegrating	2.5 mg, 5mg	10 mg
	ZOMIG	Nasal Spray	2.5 mg, 5mg	10 mg
Rizatriptan	MAXALT	Tablets	5 mg, 10mg	30 mg
	MAXALT- MLT	Orally disintegrating Tablet	5 mg, 10mg	30 mg
Naratriptan	AMERGE	Tablets	1 mg, 2.5 mg	5 mg
Almotriptan	AXERT	Tablets	6.25, 12.5 mg	25 mg
Frovatriptan	FROVA	Tablets	2.5 mg	7.5 mg
Eletriptan	RELPAX	Tablets Information currently not available		

has been extensively studied, with a mean therapeutic gain (the difference between the active and the placebo response - TG) of 33% (95% CI 29% - 36%) after 2 hours[4].The first studies on oral sumatriptan showed statistically significant effects for the 50 mg dose as early as 30 minutes when compared with placebo. For sumatriptan 25 mg, the TG is 24%[9].

Sumatriptan nasal spray provides faster onset of effect than the tablet but produces a similar headache response at 2 hours[10].The 20 mg spray demonstrated difference from placebo, at 15 minutes, in 3 of 5 placebo-controlled trials[4].The TG at 2 hours ranges from 28% to 55%. Some patients prefer the nasal spray as it works more quickly than the tablet and does not have as many adverse effects as the injection. Others do not like it, for a variety of reasons, the nasal route of administration, bad taste and inconsistency of response.

The 25 mg suppository is available in Europe and Asia. Rectal sumatriptan is superior to placebo after 30 minutes and 60 minutes, the mean TG being 31% (95% CI 25% - 37%)[11]. All forms of sumatriptan (and all other triptans) relieve the associated symptoms (nausea, vomiting, photo and phonophobia) as well as the pain of migraine[12]. As noted, the overall headache recurrence rate from sumatriptan is in the 30 to 40% range[8-10], and occasionally higher in certain studies. It appears that treating at the mild level of pain reduces headache recurrence[8].

The dose of injectable sumatriptan is 6 mg subcutaneous, which may be repeated once after 1 hour for a total of two doses/24 hours. The dose of the nasal spray is 20 mg stat, which can be repeated once after 2 hours for a total of two doses/24 hours. The dose or oral sumatriptan is a 50 mg or 100 mg tablet early in the course of a migraine attack, which can be repeated in 2 hours. The maximum oral dose is 200 mg per day in the US, 300 mg/24 hours in every other country in the world.

ZOLMITRIPTAN

Zolmitriptan was developed with the goal of creating a more lipophilic, centrally active and rapidly absorbed oral tablet than sumatriptan[13]. Its pharmacokinetic properties are displayed in Table 2. The dose is 2.5 mg or 5 mg early in the course of the migraine, and a repeat dose may be given in two hours. Maximum dose is 10 mg/24 hours in the US and by the EU regulatory authorities. Zolmitriptan demonstrates a mean headache response of 64% with a TG of 34% for the 2.5 mg dose and a mean headache response of 65% with a TG of 37% for the 5 mg dose[14]. The 2-hour pain-free response with the 5 mg dose was considerably better than that of the 2.5 mg, at 38% to 33%[4,14]. The recommended starting dose of 2.5 mg provides the best balance of benefit and side effect although some patients do obtain more complete and rapid relief from the higher 5 mg dose, a dosage only available in the US and Sweden. The recurrence rate is variable, ranging from 22 to 37%[15]. There have been three comparative trials between zolmitriptan and sumatriptan. The first, a single attack study compared zolmitriptan 5 mg to sumatriptan

Table 2. Pharmacokinetics of the Triptans.

Drug	T_{max} (h)	Lipophilicity	$T_{1/2\ (h)}$	Bioavailaility	Elimination route / Metabolism
Sumatriptan		Low	2		Hepatic; MAO-A; 60% renal
50 mg tablet	2.5			14%	renal
20 mg spray	1			17%	
6 mg s.c.	0,2			97%	
Zolmitriptan		Moderate			Hepatic (1 active and 2 inactive
2.5 mg tablet	2		2.5 – 3.0	40% - 48%	metabolites); CYP-MAO-A
2.5 mg ZMT	3.3		2.5 – 3.0	40% - 48%	
2.5 mg nasal	2		2.82	42%	
Rizatriptan	1.2 (Tablet) 1.6 – 2.5 (Melt)	Moderate	2.0 – 3.0	45%	Hepatic MAO-A; 30% excreted renally unchanged
Naratriptan	2.0 – 3.0	High	5.0 – 6.3	63% (men) 74% (women)	70% excreted renally unchanged; CYP; not MAO-A
Almotriptan	1.4 – 3.8	Unknown	3.2 – 3.7	80%	Hepatic; CYP/MAO-A; 15% active N-Demethylmetabolite 26% - 35% excreted renally unchanged
Eletriptan	1.0 – 2,0	High	3.6 – 5.5	50%	Hepatic CyP3A4; 15% active N-Demethyl metabolite; not MAO-A
Frovatriptan	2.0 – 4.0	Low	25	24% - 30%	Hepatic; CYP/MAO-A; 26% - 35% excreted renally unchanged

CYP, cytochrome P450; MAO-A, monoamine oxidase-A; $\mathbf{T_{max,}}$ time to peak plasma concentration; $\mathbf{T_{1/2}}$, half-life.

Table 3. clinical end-points for the triptans from selected clinical trials.

Drug	Dose (mg) and route	Therapeutic Gain at 2h (%)	Recurrence rate (%)
Sumatriptan	6 s.c.	51%	34 – 38
	50 oral	29% - 36%	32
	20 nasal spray	28% - 55%	32 – 34
Zolmitriptan	2.5 oral	34%	30
	2.5 ZMT	41%	
	2.5 nasal spray	26%	
	5.0 nasal spray	40%	
Naratriptan	2.5 oral	22%	17 - 28
Rizatriptan	10 oral	27% - 40%	30 – 47
	10 MLT	19% - 46%	
Almotriptan	12.5 oral	26% - 32%	18
Eletriptan	40 oral	22% – 41%	19 – 23
Frovatriptan	2.5 oral	16 – 19%	7 - 25

100 mg and found no difference for complete headache response, headache relief or pain-free state[16].The second was a 6 attack study comparing zolmitriptan 2.5 mg versus sumatriptan 25 mg and 50 mg and found the headache response at 2 hours was statistically higher for zolmitriptan 2.5 mg (67.1%) than for sumatriptan 25 mg (59.6%) or 50 mg (63.8%)[17].The third trial was done with identical methodology to the second, except zolmitriptan 2.5 and 5 mg were compared with sumatriptan 50 mg. This study showed no difference for any endpoint between the doses of medications[18]. Thus, for the primary efficacy clinical endpoints there appears to be no overall significant difference between oral zolmitriptan and oral sumatriptan in large population studies. However, zolmitriptan is the only triptan with evidence of effectiveness of a second dose when the first was not completely successful[19].

Zolmitriptan is also available, in some countries, as orally disintegrating tablet (ODT), that dissolves on the tongue within 30 seconds but is absorbed from the gastrointestinal tract. It is a convenient alternative for those patients who prefer not to take conventional tablets or who are nauseated and cannot swallow water with their pill[20]. The TG at 2h , with the 2.5 mg ODT formulation is 41%, the pain-free response at 2h being 27% vs 7% in the placebo group[4].The ODT was preferred to conventional tablets by 70% of patients, and the adverse event profile was consistent with that previously reported for the conventional zolmitriptan tablet[21].

Zolmitriptan NS has recently become available in Sweden and is expected in the U.S.. NS formulations do offer the potential pharmacokinetic advantage of more rapid drug absorption across the nasal mucous. This may be expected to confer a faster onset of action for a higher percentage of patients compared with oral treatments. In addition, intranasal administration offers a viable alternative to subcutaneous injection when oral administration is undesirable or precluded. Preliminary results of the zolmitriptan NS show a headache response of 70.2% at 2 h (TG = 40%) and pain free response of 35.9% (TG = 27.7%) for the 5 mg, according to randomized controlled trials[22]. It has a rapid onset of headache relief demonstrating significant improvement over placebo as early as 15 minutes after the dose is administered. Nasal absorption has been demonstrated by PET-scan.

NARATRIPTAN

Naratriptan was the third selective 5-$HT_{1B/1D}$ agonist to be introduced in the US for the acute treatment of migraine[23]. Oral naratriptan, available in the US in 1 and 2.5 mg tablets, differs from sumatriptan primarily in its longer half-life of 6 hours, longer T_{max} of 2 hours, higher oral bioavailability (70%) and higher lipophilicity (70%)[23]. Compared to other triptans, the 2.5 mg tablet of naratriptan, the only one available in most countries, presents a low TG at 2 hours (22%), with just about 48% of patients obtaining a headache response at 2h. The TG at 4 h is better, ranging from 26% to 34%[24].

In several studies, the incidence of adverse events with naratriptan was very low, similar to placebo, and naratriptan has been referred to as the "gentle triptan." It has not been found to have significant drug interactions[23].

Recurrence of headache with naratriptan after 4-hour headache response is also low, ranging from 17% to 28%. When compared directly with sumatriptan and rizatriptan,

Table 4. Clinical features of the Group I and Group II triptans.

	Group I	Group II
Features	Faster onset	Slower onset
	Higher potency	Lower potency
	Higher recurrence	Lower recurrence
Triptans	Sumatriptan	Naratriptan
	Zolmitriptan	Frovatriptan
	Rizatriptan	
	Almotriptan	
	Eletriptan	

naratriptan showed lower recurrence rates[25].

The probability of taking rescue medication after a first dose of naratriptan is low and similar to dihydroergotamine[22,25].

Thus, naratriptan has a more gentle adverse effect profile, and a lower recurrence rate when directly compared with other triptans, but it has a lower percent effectiveness at two and four hours after dosing. The dose is 2.5 mg given early in the course of the migraine attack, which may be repeated at two to four hours if the headache is not significantly better, to a maximum of 5 mg/24 hours.

RIZATRIPTAN

Rizatriptan was synthesized also in the hope of creating a faster acting, more lipophilic tablet[26]. The drug is available in two oral dosage strengths of 10 mg and 5 mg, with 10 mg being the recommended starting dose in most countries. It can be repeated after 2 hours if the headache persists. Rizatriptan is also available as an ODT that can be taken without liquids, in the same dosages.

Rizatriptan has a high oral bioavailability of 45%. The half-life is 2 to 3 hours and the T_{max} is 1.3 hours for the conventional tablet and slightly longer for the ODT (Table 2)[27]. Placebo-controlled studies for the 10 mg tablet found a 2-hour TG ranging from 27% to 40%, with headache relief at 2 hours (70 to 77%) and a pain-free response at 2h ranging from 40% to 44% (Placebo response ranging from 2 to 10%).The recurrence rate for the 10 mg tablet ranges from 30% to 47%[28,29].

As with the zolmitriptan ODT, the rizatriptan ODT is not absorbed from the mucous membrane of the mouth but rather dissolves in, and is subsequently swallowed with saliva for a further gastrointestinal absorption. The 2-h TG for this formulation ranges from 19% to 46%[27].

There is clear evidence from direct comparisons with sumatriptan, zolmitriptan, and naratriptan that rizatriptan 10 mg is more likely to achieve a pain free outcome at 2 hours and sustained 2 hour pain free response.[28] Tfelt-Hansen and Ryan[29] reviewing clinical trials comparing rizatriptan and sumatriptan, concluded that five mg rizatriptan was comparable to 50 mg sumatriptan. Rizatriptan 10 mg, the recommended dose in most countries, had a more rapid onset of action than 50 mg and 100 mg sumatriptan. In addition, 10 mg rizatriptan resulted in more patients being pain-free after 2 hours than 100 mg sumatriptan and resulted in fewer drug-related adverse events than sumatriptan. Rizatriptan 10 mg, in a head to head comparison to naratriptan 2.5 mg, showed statistical superiority in all end points at 2 hours, but the recurrence rate was lower with naratriptan[27].

Rizatriptan 10 mg was also directly compared with zolmitriptan 2.5 mg[27]. Rizatriptan was superior to zolmitriptan at 2 h for pain free response. Since the optimal dose for zolmitriptan to achieve a 2 hour pain free response is 5 mg (see above), comparable doses may not have been used in this comparative study. However, since the 5 mg dose is only available in two countries, the commercially available doses and recommended starting doses were compared.

In summary, rizatriptan is a fast-acting oral triptan, with the highest pain free and sustained pain free responses of the available triptans, and with a recurrence rate comparable with that of oral sumatriptan and zolmitriptan, but higher than naratriptan.

ALMOTRIPTAN

Almotriptan is a new 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} agonist[30].The bioavailability of oral almotriptan is around 70%. Even though the T_{max} is 2.5 hours, the absorption of almotriptan seems to be rapid, with more than two-thirds of the drug reaching the plasma within the first hour of the oral administration[30].

Clinical trials show a clear dose-response relationship for almotriptan, 6.25 mg being the minimum effective dose, 12.5 mg the ideal therapeutic dose with the most favorable relationship between efficacy and tolerability, and 25 mg being the most effective of therapeutic doses in clinical trials. The 12.5 mg dose shows significant onset of efficacy over placebo between 30 and 45 min. The TG for pain relief at 2 h ranges from 26% to 32%; the therapeutic gain for the pain free state at 2h ranges from 20% to 23%. The recurrence rate is between 18% – 29%[31]. In controlled trials, the overall incidence of drug-related adverse experiences with almotriptan 12.5 mg and placebo was 16% and 15%, respectively[30,31].

There was no difference between almotriptan 12.5 mg and sumatriptan 100 mg directly compared, for primary efficacy measures and recurrence except for a superiority for sumatriptan 100 mg over almotriptan 12.5 mg for pain free at 2 hours[32].

Almotriptan appears to be superior to sumatriptan regarding tolerability with lower AEs such as chest pain when directly compared in one study[30-32]. This does not mean that almotriptan is safer, as chest symptoms are rarely cardiac in origin.

The optimal dose for almotriptan is a 12.5 mg tablet at the start of a migraine headache, which may be repeated once in 2 hours to a maximum of 25 mg/24 hours.

ELETRIPTAN

Oral eletriptan has a very short T_{max} of 1 to 2 hours with a relatively long half-life of 3.6 to 5.5 hours. It has a

50% oral bioavailability[33] (Table 2). Eletriptan may interact with other compounds that are metabolized by the cytochrome (CYP) P-450 3A4 hepatic enzymatic system. Concomitant administration of eletriptan with CYP 3A4 metabolized medications causes a rise in the eletriptan plasma levels[34]. The concern is that higher blood levels of eletriptan could cause an increase in AE's. In the EU prescribing information eletriptan is not supposed to be used with potent CYP 3A4 metabolized medications such as macrolide antibiotics (e.g. erythromycin, clarithromycin), antifungals (e.g. fluconazole) and certain antivirals. According to pooled abstract data presented by Pfizer from two long-term studies, the incidence of adverse events was similar whether or not patients took CYP 3A4 inhibitors in combination with either eletriptan 40 mg or 80 mg. Even the concomitant use of potent CYP 3A4 inhibitors did not influence the incidence of reported adverse events in these studies[34].Thus the concomitant use of CYP 3A4 inhibitors may not decrease the tolerability of eletriptan, but clinicians should be cautious about co-prescribing eletriptan and significantly CYP 3A4 metabolized medications pending publication of full safety data.

The TG of eletriptan 40 mg at 2 h ranges from 22% to 41%. The TG of eletriptan 80 mg ranges from 30% to 53%[33]. Headache recurrence seems to occur in about one third of patients in some studies, similar to sumatriptan, but is considerably lower in other studies[33].

To date, only two peer-reviewed studies on eletriptan have been published. The first one was conducted by Goadsby et al[35].They compared the efficacy, safety and tolerability of oral eletriptan (20 mg, 40 mg and 80 mg) with 100 mg of encapsulated sumatriptan, in a double-blind, placebo controlled study. Two hours after dosing, headache response rates were 24% for placebo, 55% for sumatriptan 100 mg, 54% for eletriptan 20 mg, 65% for eletriptan 40 mg and 77% for eletriptan 80 mg. Headache-free rates at 2 hours were superior to placebo for both the 80 mg dose of eletriptan (37%) and the 40 mg dose (29%), with the 80 mg dose also being superior to sumatriptan 100 mg (23%). AEs occurred in 17% of the patients who received placebo, 40% who received sumatriptan, 34% who received eletriptan 20 mg, 35% who received eletriptan 40 mg and 51% who received eletriptan 80 mg. The majority of AEs were mild or moderate in intensity and transient.

The second peer-reviewed study, on behalf of the Eletriptan Steering Committee[36] evaluate the efficacy, safety and tolerability of eletriptan (40 mg and 80 mg) in a double-blind, placebo-controlled, three attack study treating 1,153 patients. In the initial attack, significantly more eletriptan patients reported headache relief and complete pain relief at 2 h vs. placebo (40 mg, 62% and 32%; 80 mg, 65% and 34%; placebo, 19% and 3% - $p < 0.0001$). More patients that received both doses of eletriptan reported relief at 30 min ($p < 0.01$). There was a significantly lower recurrence rate with eletriptan 80 mg compared with placebo (21% vs. 40%, $p < 0.01$). The recurrence rate of the 40 mg dose did not reach statistical significance (30%). Adverse events for all treatments were mild or moderate and self-limited. They concluded that eletriptan 40 mg and 80 mg appear to be effective and well-tolerated acute migraine treatments.

In the EU, eletriptan is approved in 20 and 40 mg doses. After two out of three well tolerated failures, patients have the option of taking two 40 mg doses at the onset of an attack, but maximum dosage/24 hours is 80 mg. In some countries (i.e. the Czech Republic) 40 mg and 80 mg tablets are available.

FROVATRIPTAN

Frovatriptan is an unusual triptan with an extremely long half-life of 26 hours[37]. This is the longest half-life of any agent in the triptan class, where the other half-lives range from 2h to 6h. Like naratriptan and almotriptan, frovatriptan also has a dual route of elimination via both the kidney and liver (cytochrome P450 1A2). There is no metabolism via the MAO system. The pharmacokinetics of frovatriptan are not significantly altered by drugs such as propranolol, moclobemide, other antidepressants and ergotamine[37].

Frovatriptan 2.5 mg is the optimal dose. The maximum dose/24 hours is 7.5 mg. Headache response at 2 h is 37% – 46%. The TG at 2 h ranges from 16% to 19%, and at 4h from 25% to 27%[38]. There is a paucity of peer-reviewed studies on frovatriptan, so most information is only available in abstract form.

Frovatriptan has the lowest range of 24-hour headache recurrence among the triptans, from 7% to 25% when compared to placebo. However, when directly compared with sumatriptan 100 mg, there was no significant difference in recurrence rate. This suggests yet again that recurrence rate may not be related to half-life[38].

During short and long-term clinical trials, again available only in abstract form, the number of adverse events for frovatriptan 2.5 mg was just marginally higher than that found for placebo. In a direct comparison with sumatriptan 100 mg, the overall incidence of adverse events with frovatriptan was significantly lower than with sumatriptan (36% vs 43%, $p = 0.03$)[37,38].

TRIPTANS ARE NOT THE SAME

Different triptans are available in different strengths and formulations including oral tablets, orally disintegrating tablets, nasal sprays and subcutaneous injections (table 1 and table 3). In Europe, sumatriptan is also available as a suppository. Specific differences among the triptans exist as evidenced by different pharmacological profiles including $T_{½}$, T_{max}, C_{max}, AUC, metabolism, drug-drug interaction profiles, amongst other parameters[39]. How or whether these differences translate to clinical efficacy and tolerability differences is not well differentiated. Clinical distinctions among these agents are subtle and proper choice of triptan requires attention to the specific characteristics of each individual patient, knowledge of patient

preference, accurate history of the efficacy of previous acute care medications as well as individual features of the drug being considered.

Delivery systems may play an important role in the onset of action of triptans. Subcutaneous delivery of sumatriptan offers the most rapid and complete pain relief of the triptans beginning as early as 10 to 15 minutes, yet it also is associated with a higher incidence of adverse events. The second most rapid onset of action of the triptans is achieved through NS deliveries of sumatriptan and zolmitriptan, but the percentage of headache relief at 2 hours is not as high as with the subcutaneous delivery formulation. All of the triptans are available as conventional tablets, and two (rizatriptan and zolmitriptan) are also available in ODTs. ODT's are more convenient to use and can be taken when the patient is nauseated; they do not work any faster than tablets, and their gastrointestinal absorption means that they will not be absorbed if vomiting occurs soon after ingestion.

Beside delivery options, other clinical distinctions to consider among the triptans are the percentage of patients attaining headache relief. The oral triptans can be divided into two groups (Table 4). Group I consists of the oral triptans with faster onset and higher potency, namely sumatriptan, zolmitriptan, rizatriptan, almotriptan, and eletriptan. Group II consists of the slower onset oral triptans with lower overall potency and lower recurrence. These are naratriptan and frovatriptan. Within each oral group, responses in populations studied are more similar than different.

Some brief specific characteristics of the individual triptans are[39]: 1) Sumatriptan has been available for the longest time, is most flexible in form, and has been given successfully to the most number of patients; 2) Zolmitriptan is the only triptan proven effective when repeated for a persistent headache; 3) Naratriptan has a slower onset of action but a most favorable adverse event profile and a lower recurrence rate, which may help address the clinical challenges of treating long migraine attacks; 4) Rizatriptan has the highest 2-hour pain free rates and sustained pain free rates and the fastest time to headache response rate for an oral tablet; 5) Almotriptan has a slightly better side effect profile with somewhat less chest pain than sumatriptan; 6) Eletriptan has a clear dose response curve and may be associated with good sustained headache response rates; 7) Frovatriptan is a slower acting triptan with the longest half life in the class. As noted above, in spite of these differences, the oral triptans within each group are more similar than different but, importantly, one cannot predict which triptan will work best for any given patient[39]; the patient should be questioned carefully to determine if the triptan taken is ideal in terms of rapid onset of action, complete response to attain the pain free state, consistency, lack of recurrence, tolerability and minimal side effects. Adverse event profiles are usually not helpful in determining which triptan is best matched for a particular patient, unless the patient has significant and intolerable adverse effects from previous triptans, in which case naratriptan or almotriptan would be the obvious choices.

SAFETY AND TOLERABILITY

Safety needs to be distinguished from tolerability. Tolerability involves adverse events that are irritating but not generally considered as clinically significant, such as nausea or dizziness. Safety implies no clinically significant adverse events, such as myocardial infarction, stroke, or hepatic toxicity.

The triptans as a class are generally very well tolerated, with less than half of patients reporting adverse events, mostly mild in intensity and transient. Most of the triptans show a modest increase in the incidence of adverse events at higher doses[39,40].

Overall, naratriptan, almotriptan and frovatriptan appear to have the most favorable adverse event profiles. It should be emphasized, though, that tolerability problems as a reason for medication discontinuation are relatively low for all triptans.

For the triptans as a class there is a very low but definite potential risk of significant coronary vasoconstriction[40] . Extensive use of triptans over the past decade has provided substantial reassurance that the risk is very minimal, which is consistent with data suggesting that 5-HT_{1B} receptors mediate less than 25% of the overall vasoconstrictive potential of the coronary arteries. Parenteral challenge with sumatriptan has been reported to result in approximately 14% coronary vasoconstriction.[40] It should be noted that the differential vasoconstrictive selectivity of triptans is partly due to the significantly higher density of 5-HT_{1B} receptors in the meningeal arteries compared to the coronary arteries. All triptans appear to be relatively safe in the absence of coronary artery disease, any other significant vessel disease, uncontrolled hypertension and the presence of cardiac risk factors. But there is no "safest" triptan since no triptan is without some risk, and it should be emphasized that all are contraindicated in the presence of significant vascular disease.

CONCLUSIONS

When treating an acute migraine attack, clinicians have a wide variety of triptans with different pharmacokinetics characteristics, routes of administration and significant clinical endpoints on various types of studies to choose from and must decide how to select, sequence and combine these acute treatment options. The introduction of the triptans in the 1990s was a major breakthrough in the treatment of migraine, changing millions of lives for the better. Continued clinical use will yield familiarity with the various triptans, and it should become possible for the interested physician to match individual patient needs with the specific characteristics of a triptan to optimize therapeutic benefit.

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