Eletriptan in the management of acute migraine: an update on the evidence for efficacy, safety, and consistent response

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***Abstract*:** Migraine is a multifactorial, neurological and disabling disorder, also characterized by several autonomic symptoms. Triptans, selective serotonin 5-$HT_{1B/1D}$ agonists, are the first-line treatment option for moderate-to-severe headache attacks. In this paper, we review the recent data on eletriptan clinical efficacy, safety, and tolerability, and potential clinically relevant interactions with other drugs. Among triptans, eletriptan shows a consistent and significant clinical efficacy and a good tolerability profile in the treatment of migraine, especially for patients with cardiovascular risk factors without coronary artery disease. It shows the most favorable clinical response, together with sumatriptan injections, zolmitriptan and rizatriptan. Additionally, eletriptan shows the most complex pharmacokinetic/dynamic profile compared with the other triptans. It is metabolized primarily by the CYP3A4 hepatic enzyme and therefore the concomitant administration of CYP3A4-potent inhibitors should be carefully evaluated. A relatively low risk of serotonin syndrome is given by the co-administration with serotoninergic drugs. No clinically relevant interaction has been found with drugs used for migraine prophylactic treatment or other acute drugs, with the exception of ergot derivatives that should not be co-administered with eletriptan.

Keywords: acute migraine, efficacy, eletriptan, safety

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Introduction

Migraine is a common and complex disease, with an estimated prevalence of about 10–15% of the population worldwide [Smitherman *et al.* 2013]. It is characterized by recurrent headache pain that can be accompanied by several autonomic symptoms, such as nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia) [Burstein *et al.* 2015]. Migraine can be exacerbated by a number of triggers, such as physical activity, specific kinds of food or alcohol intake, hormonal changes and stress [Sauro and Becker, 2009; Hoffmann and Recober, 2013]. Moreover, in about one-third of cases, headache attacks might be preceded by the aura, comprising fully reversible sensory, visual or dysphasic symptoms [International Headache Society, 2013]. Migraine has a high impact on patients' quality of life, causing both short- and long-term disability, lowering work productivity and affecting social relationships and family life [Baigi and Stewart, 2015]; therefore efforts should be made to find an appropriately effective treatment for each patient. In fact, a large number of medications are available for both acute and preventive migraine treatment that should be individualized and tailored to the patient's clinical features [Becker, 2015]. Triptans represent the first-line abortive treatment for moderate-to-severe migraine attacks and mild-to-moderate attacks that failed to respond to analgesics and anti-inflammatory drugs [Gilmore and Michael, 2011]. The triptan family consists of seven molecules (sumatriptan, zolmitriptan, eletriptan, naratriptan, rizatriptan, almotriptan, frovatriptan) that, despite the biochemical similarity, show a definite and distinctive pharmacokinetic and pharmacodynamic profile [Jhee *et al.* 2001]. Because of their longer half-lives, naratriptan and frovatriptan have a delayed onset of action with a more prolonged duration compared with the other fast-acting triptans, that display a rapid dose-dependent efficacy with a higher risk of adverse

Table 1. Triptan's pharmacodynamic and pharmacokinetic features.

	Sumatriptan	Eletriptan	Zolmitriptan	Almotriptan	Naratriptan	Rizatriptan	Frovatriptan
Targets	5-HT_{1D} 5-HT_{1B} 5-HT_{1F} 5-HT_{1A}	5-HT_{1D} 5-HT_{1B} 5-HT_{1F} 5-HT_{1A} 5-HT_{1E} 5-HT_{2B} 5-HT_{7}	5-HT_{1D} 5-HT_{1B} 5-HT_{1F} 5-HT_{1A}	5-HT_{1D} 5-HT_{1B}	5-HT_{1D} 5-HT_{1B} 5-HT_{1F} 5-HT_{1A}	5-HT_{1D} 5-HT_{1B} 5-HT_{1F}	5-HT_{1D} 5-HT_{1B}
Enzymes	MAO-A [S]	CYP3A4 [S,Inh] CYP2D6 [S] CYP2C9 [S] CYP2C19 [S] PTGS1 [S] CYP2A6 [Ind]	CYP1A2 [S] MAO-A [S]	CYP3A4 [S] CYP2D6 [S] CYP1A2 [S] CYP2C19 [S] CYP2E1 [S] CYP2C8 [S] MAO-A [S] FMO3 [S]	MAO-A [S]	MAO-A [S] CYP1A2 [S]	CYP1A2 [S]
Transporters	SLCO1A2 [Ind] MRP1 [Inh] ABCG2 [S] SLCO1B1 [S]	MRP1 [S]	–	–	–	–	–
Half-life	2.5 hours	4 hours	3 hours	3–4 hours	5–8 hours	2–3 hours	26 hours
Bioavailability	15%	50%	40%	70%	74%	45%	20–30%
Protein binding	14–21%	85%	25%	35%	28–31%	14%	15%

5-HT, 5-hydroxytryptamine; MAO-A, monoaminooxigenase-A; CYP, cytocrome P450; PTGS, prostaglandines G/H synthase; FMO, dimethylaniline monooxygenase [N-oxide-forming]; SLCO, solute carrier organic anion transporter; MRP, multidrug-resistant protein; ABCG, ATP-binding cassette subfamily G; [S], substrate; [Ind], inducer; [Inh], inhibitor. Pharmacokinetic data for sumatriptan are related to the oral formulation.

effects and migraine recurrence [Markus and Mikko, 2007; Negro *et al.* 2011]

Triptan selection for each patient is a complex process that should take into account several variables: the characteristics of migraine attacks (speed of onset, intensity of pain, duration of the attack), the drug onset of action, the individual patient response and tolerance, the relief of associated symptoms, the headache recurrence, the consistency of the response, the different delivery systems and the patient characteristics (medical history, lifestyle and working habits) [Belvìs *et al.* 2009]. Although the choice of a specific treatment is based mainly on the drug efficacy and safety profile, and therefore on its pharmacokinetic and pharmacodynamic properties [Géraud *et al.* 2003], recently, the role of inherited and acquired genetic variations in drug response has also been highlighted [Gentile *et al.* 2011; Negro *et al.* 2011]. As shown in Table 1, eletriptan shows the most complex pharmacokinetic/dynamic profiles among triptans and therefore a possible higher chance of bio and drug interactions (see http://www.drugbank.ca/). In this review, we will discuss with a systematic approach the eletriptan pharmacodynamic and pharmacokinetic features, considering the emerging data on its clinical efficacy, safety and tolerability profile in the treatment of migraine [Mathew *et al.* 2003a]. We searched the Medline/PubMed and EMBASE databases for citations of studies reported in English with no time limits. Additional citations were identified in the bibliographies of published reports. The terms used as search keywords were 'eletriptan' and 'pharmacokinetics', 'pharmacodynamics', 'interactions', 'clinical efficacy', 'safety', 'side effects', 'comparative trial'. Abstracts of reports, so identified, were inspected independently by three reviewers with research experience in the clinical study of eletriptan. Reports included for detailed review and analysis were required to link eletriptan treatment with significant clinical efficacy, safety, tolerability and drug interactions data. We did not include all nonclinical studies.

Eletriptan biochemical and pharmacological features

Eletriptan is a relatively new drug, approved by the US Food and Drug Administration (FDA) on

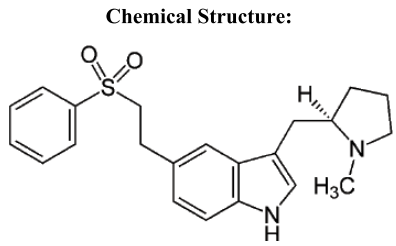

Figure 1. Eletriptan chemical structure.

26 December 2002, for the acute treatment of migraine with or without aura in adults. Eletriptan is a methylpyrrolidinyltryptamine substituted with a benzene sulfonyl derivative and belongs to the class of organic compounds known as indoles (Figure 1). Its chemical name is (R)-3-(1-methyl-2-pyrrolidinylmethyl)-5-(2-phenylsulphonyl) ethyl-1H-indole and it has a molecular weight of 382.52 Daltons.

It shows a rapid and consistent absorption, high oral bioavailability and a potent activity as a 5-hydroxytryptamine 1-receptor subtype B/D ($5\text{-HT}_{1B/1D}$)-receptor agonist [Sandrini *et al.* 2009]. It has a proven efficacy profile for the acute treatment of moderate-to-severe migraine headache attacks, with a high safety and tolerability profile regardless of age and sex, for both short- and long-term treatment [Mathew *et al.* 2003a]. Eletriptan is commercially available at doses of 40 mg or 80 mg, and has been demonstrated to be effective nearly 30 minutes after the administration. In comparative clinical trials (discussed below) eletriptan (40 and 80 mg) showed superior or equivalent efficacy to other triptans with high safety and tolerability [McCormack *et al.* 2006], and the most favorable cost effectiveness when compared with other drugs in its class [Sandrini *et al.* 2009; Bhambri *et al.* 2015].

Pharmacodynamics

Marketed triptans, including eletriptan, are characterized by a potent and highly selective affinity (pKi = 8–9) for 5-HT_{1B} and 5-HT_{1D} receptors, involved in the pathophysiology of migraine (Table 1). In fact, 5-HT_{1B} and 5-HT_{1D} activation has a vasoconstrictive action in painfully dilated cerebral blood vessels, an inhibitory action on vasoactive neuropeptide release by trigeminal nerves and reduces nociceptive neurotransmission [Tepper *et al.* 2002]. Eletriptan, similarly to the other triptans, with the exception of frovatriptan and almotriptan, has also agonist activity for the human 5-HT_{1F} receptor (Table 1) [Jähnichen *et al.* 2004]. The functional significance of 5-HT_{1F} receptors still remains partly unknown, even if their capability to inhibit the activation of second-order neurons, and therefore the transmission of nociceptive information, within the trigeminal nucleus caudalis (TNC) has been demonstrated [Shepheard *et al.* 1999]. Moreover, 5-HT_{1F} mRNA has been found in the trigeminal ganglion and human cerebral and coronary arteries, suggesting a potential role of these receptors in cerebrovascular functions and dural inflammation, with a potential involvement in migraine pathogenesis [Bouchelet *et al.* 1996]. Eletriptan affinity with unknown pharmacological action has also been demonstrated for 5-HT_{1A}, 5-HT_{1E}, 5-HT_{2B}, and 5-HT_{7} [Johnson *et al.* 2001].

Eletriptan has no clinically significant activity at any other pharmacologic targets (e.g. 5-HT_{3}, 5-HT_{4}, 5-HT_{5A}, 5-HT_{6}, α_1, α_2, or β-adrenoceptors; adenosine A1, dopamine D1, or D2, muscarinic, histaminic) (Table 1). This lack of affinity at other receptors is the pharmacologic basis for the high degree of safety and tolerability of the triptan class [Mathew *et al.* 2003a].

The putative mechanisms of eletriptan therapeutic action in migraine are multiple: (i) it has a vasoconstrictive action on dilated meningeal blood vessels; (ii) in perivascular trigeminal sensory neurons it inhibits the release of vasoactive neuropeptides and (iii) reduces the pain signal transmission in the trigeminal dorsal horn [Derry *et al.* 2010]. The vasoconstrictive action has been demonstrated *in vitro* for isolated canine and human arteries, and the vasoconstriction of isolated human meningeal artery with a potency similar to that of sumatriptan (EC_{50} = 50 nm) has been demonstrated. Notably, eletriptan is greatly less potent in inducing vasoconstriction of isolated human coronary artery (EC = 4299 nm) [Milton *et al.* 2002]. Therefore, eletriptan is considered a selective vasoconstrictive drug for the intracranial blood vessels compared with the other extracranial vessels, and in particular with coronary arteries [Diener and McHarg, 2000].

Pharmacokinetics

Eletriptan is orally administered in tablets of 20 mg and 40 mg, with a maximum daily dose of 80 mg [Derry *et al.* 2010]. The absorption,

central nervous system penetration and volume of distribution are higher than those of the other triptans, given the greater lipophilicity of eletriptan [+0.5 (log D at pH 7.4)] [Sandrini *et al.* 2009]. After oral intake, the absorption from the gastrointestinal tract is rapid, and the mean time to maximum concentration (T_{max}) is about 2 hours during an acute migraine attack. The bioavailability is around the 50%, the maximum plasma concentration (C_{max}) around 188–234 ng/ml, the protein binding approximately 85%, and the half-life is relatively long (3.6–5.5 hours) [Shah *et al.* 2001]. Brain penetration by eletriptan is limited by the active P-glycoprotein (P-gp), the blood–brain–barrier efflux system that removes lipophilic drugs from the central nervous system [Evans *et al.* 2003]. In fact, the P-gp efflux pump has been demonstrated both to modulate the eletriptan oral exposure and to reduce the brain exposure by approximately 40-fold, accounting for the large administered oral dose.

Pharmacokinetic parameters are linear over the clinical-dose range, and are not affected by age, sex, race or time in the menstrual cycle. Eletriptan clearance is mainly nonrenal, and about 90% is eliminated by metabolism (principally hepatic) [Belvis *et al.* 2014]. The cytochrome P-450 system is responsible for the hepatic metabolism of eletriptan, and primarily from the CYP3A4 enzyme, with a minor contribution of the other CYP enzymes. The only known active metabolite of eletriptan, *N*-desmethyleletriptan, is generated during hepatic metabolism and shows a plasma concentration of about the 10–20% of the parent drug.

Eletriptan may interact with substrates, inhibitors and inducers of the CYP3A4 enzyme. In fact, the co-administration of eletriptan with other medications able to modify CYP3A4 function might increase or decrease eletriptan plasma levels, with increased risk of development of adverse effects or reduced clinical efficacy [Takiya *et al.* 2006]. The co-administration of maximum doses of eletriptan and ketoconazole, a potent CYP3A4 inhibitor, was associated with a 2.7 fold C_{max} increase and a 6-fold increase in the area under the curve (AUC) [Mathew *et al.* 2003a]. As expected, the C_{max} and AUC of eletriptan were decreased when co-administered with mild or moderate CYP3A4 inhibitors (fluconazole, erythromycin, and verapamil). Although it is a substrate, eletriptan is not able to inhibit or induce any CYP enzyme and therefore it has no clinically relevant interactions with other medications [Mathew *et al.* 2003a].

Eletriptan metabolism by the prostaglandin G/H synthase 1 (or cyclooxigenase-1) has been also reported [Zhou *et al.* 2009]. Notably, frovatriptan and eletriptan are the only triptans not metabolized by monoamino-oxydase 1, thus, have no risk of interaction with drugs acting on these enzymes (Table 1).

Clinical Efficacy

Triptans

Triptans are considered the first-line option for the treatment of moderate-to-severe acute migraine and for the mild-to-moderate acute migraine attacks with poor response to nonsteroidal anti-inflammatory drugs (NSAIDs) or combinations of other analgesics. Principal contraindications to triptan prescription are ischemic cardiac, cerebrovascular or peripheral vascular diseases and pregnancy [Belvis *et al.* 2014]. Triptan efficacy in treating acute migraine attacks has been proven from the results of about 100 double-blind, randomized trials. Efficacy has been evaluated mainly through the parameters 'pain free after 2 hours', 'headache response', 'sustained pain-free response', 'headache recurrence' and 'rescue-medication use', even if the complete response (headache disappearing after 2 hours, with no recurrence in the next 24 hours) is the preferred effect appreciated by patients [Nett *et al.* 2007]. For this reason, the International Headache Society (IHS) suggests that a complete response should be the standard parameter by which to evaluate drugs for migraine attacks [Belvis *et al.* 2014]. However, key outcomes, such as speed and duration of pain relief, improvement in migraine-associated symptoms and risk of side effects also influence patients' satisfaction.

The seven marketed triptans have shown relief with or without absence of pain after 2 hours and a decrease of rescue-medication use if patients are treated early, when headache begins. Moreover, they have shown clinical efficacy in the reduction of the migraine-associated symptoms, such as nausea, vomiting, photophobia and phonophobia [Bigal *et al.* 2009]. Patients who experience inefficacy with single administration might also use an additional dose that is effective in about the 15–40% of cases [Ferrari *et al.* 1994; Belvis *et al.* 2014].

Eletriptan: efficacy versus placebo

Eletriptan has demonstrated a consistent and significant clinical efficacy and a good tolerability profile in the treatment of migraine. The clinical efficacy of eletriptan at suggested dosages has been compared in several trials (head to head and placebo) for the treatment of moderate-to-severe acute migraine attacks.

In a placebo-controlled trial of one migraine attack treated with eletriptan, it was superior against placebo at all available dosages (20, 40 and 80 mg) for headache relief at 2 hours. All the doses were superior to the placebo response of 51%, and 20, 40 and 80 mg sustained a 2-hour headache relief of 64%, 67%, and 76%, respectively [Stark *et al.* 2002]. Eletriptan 20 and 40 mg were studied *versus* placebo in another trial for one migraine-attack treatment and showed headache-free rates at 2 hours, 35% for 20 mg, and 47% for 40 mg, with a placebo response of 22% [Brandes *et al.* 2005]. In patients with moderate headache, the 40 mg dose showed a 2-hours headache-free rate of 68% compared with the 25% of placebo. Another placebo-controlled study showed that eletriptan 20, 40 and 80 mg doses had a 2-hour headache-relief rate of 47%, 62% and 59%, respectively, compared with a placebo response of 22% [Sheftell *et al.* 2003]. In the same study, the pain-free responses at 2 hours were 14%, 27%, and 27% for the 20, 40 and 80 mg eletriptan doses, respectively, with a placebo headache-free response of 4% [Sheftell *et al.* 2003]. An additional placebo-controlled study of eletriptan doses of 40 and 80 mg showed similar rates of headache relief and freedom after 2 hours (40 mg: 62% headache relief, 32% headache freedom; 80 mg: 65% headache relief, 34% headache freedom; placebo: 19% headache relief, 3% headache freedom) [Stark *et al.* 2002]. Moreover, the efficacy and tolerability of the three doses of eletriptan (*versus* placebo) were demonstrated to be similar in triptan-naïve and triptan-experienced patients, indicating that the previous treatment status does not influence eletriptan response [Martin *et al.* 2007]. In a recent multiple-attacks study, eletriptan 40 and 80 mg were significantly more effective in achieving a 2-hour headache response than placebo (response rate: 72.5% for eletriptan 40 mg, 70% for eletriptan 80 mg and about 23% for placebo) with a low adverse-event rate for both doses [Almas *et al.* 2014; Marmura *et al.* 2015]. Compared with all the marketed triptans, eletriptan was found to be among the most effective in two meta-analytic studies of published placebo-controlled trials [Bhambri *et al.* 2015]. In a meta-analysis of 53 trials, rizatriptan 10 mg, eletriptan 80 mg and almotriptan 12.5 mg showed the highest probability of a significant clinical therapeutical effect [Ferrari *et al.* 2001]. Moreover, the most recent meta-analysis of 74 trials showed eletriptan 40 mg to have superiority for at least one of the two considered outcomes (pain-free response at 2 hours, sustained pain-free response at 24 hours, headache response at 2 hours, and sustained headache response at 24 hours), compared with all the other triptans. In particular, eletriptan had the highest probability of patients being pain-free both at 2 hours and at 24 hours [Thorlund *et al.* 2014; Bhambri *et al.*2015].

Eletriptan: efficacy in head-to-head studies

A recent systematic review and network meta-analysis of 133 randomized controlled trials that compared triptans with placebo-controlled or active migraine treatments showed that triptan standard doses provided a headache-free response in 42–76% of patients and a sustained headache-free response in 29–50% of patients with a rescue-medication-use rate of about 27% [Cameron *et al.* 2015]. Considering the outcome headache-free response at 2 hours, triptan standard doses gave better results than ergot's (42–76% and 38% response, respectively) and equal or better responses than NSAIDs, aspirin and acetaminophen [Cameron *et al.* 2015; Diener *et al.* 2002]. Moreover, eletriptan tablets, together with sumatriptan subcutaneous injection and rizatriptan and zolmitriptan, showed the most favorable responses among all triptans [Cameron *et al.* 2015]. Compared with zolmitriptan, eletriptan 80 mg, but not 40 mg, showed significant superiority when considering the 2-hour headache-response outcome. Nevertheless, eletriptan 40 mg showed a significantly lower recurrence rate and need for rescue medication over 24 hours [Steiner *et al.* 2003]. Eletriptan (40 mg) also showed a superior clinical efficacy (with the same tolerability profile) compared with naratriptan (2.5 mg). In fact, both 2-hours pain-free response and sustained headache-free response results were higher and use of rescue medications lower in the eletriptan group [Garcia-Ramos *et al.* 2003]. Three comparative studies have been performed with sumatriptan (50 or 100 mg) and eletriptan at different doses (20, 40, or 80 mg). The results of these trials consistently showed eletriptan's (40 and 80 mg) clinical

efficacy and onset of action to be superior when compared with oral sumatriptan 100 mg. Both sumatriptan and eletriptan were well tolerated, with low incidence of adverse effects [Goadsby *et al.* 2000; Mathew *et al.* 2003b; Sandrini *et al.* 2002]. Moreover, eletriptan (compared with placebo) has been demonstrated as effective in treating acute migraine in previous nonresponders, or patients not tolerant to sumatriptan [Färkkilä *et al.* 2003]. Other triptan-switch studies reported eletriptan 40 mg efficacy in migraineurs who did not also respond to treatment with rizatriptan and NSAIDs [Bhambri *et al.* 2015].

Poor responders to low doses of eletriptan after three consecutive migraine attacks were able to achieve a 2-hour response rate of 42.5–60% on the next three attacks when the dose of eletriptan was increased to 80 mg. Therefore, a dose escalation should be considered as an effective strategy in approximately 50% of individuals, even if they are nonresponders to three consecutive attacks at a lower dose [Landy *et al.* 2014; Almas *et al.* 2014].

Tolerability and safety

The varying affinity for 5-HT receptors shown by the different triptans might not be relevant to the antimigraine efficacy, but might affect their tolerability profile. Moreover, pharmacokinetic parameters of each drug, such as bioavailability, lipophilicity, or metabolism are also relevant for safety and tolerability. Some of the most common adverse effects of triptan-family drugs include sleepiness or fatigue, difficulty in thinking, tachycardia and dizziness [Dodick and Martin, 2004].

Eletriptan has been reported in literature as a safe and tolerable drug. The most common adverse effects are usually transient and associated with the eletriptan central nervous system (CNS) activity, such as dose-related somnolence, dizziness, asthenia, and nausea [Sandrini *et al.* 2009]. With regards to relevant clinical change in chemistry and vital parameters, no significant alterations have been reported in patients treated with eletriptan [Shah *et al.* 2002]. A common effect is a transient increase in mean systolic and diastolic blood pressure after 1 hour from eletriptan administration, reflecting the time of its C_{max}. It has been shown that the increase in diastolic blood pressure is related to the eletriptan dose, whereas the association of systolic blood-pressure rise and dosage appears less strong [Shah *et al.* 2002]. Reported severe adverse events were generally uncommon, and almost all related to cardiovascular acute diseases (acute myocardial infarction, arrhythmias, cerebrovascular events), especially in patients suffering from previous cardiovascular disorders. The occurrence of myocardial infarction attributable to eletriptan overdose in a patient without coronary artery disease has been recently reported but, to best of our knowledge, it is a unique case. Notably, eletriptan has been demonstrated in animals to induce coronary constriction at four times higher dose than sumatriptan [Muir *et al.* 1999]. Therefore, it represents the triptan of choice in patients with cardiovascular risk factors, without coronary artery disease. In any case, patients should be educated to not to exceed the indicated dose and to recognise early clinical symptoms of angina [Dias *et al.* 2014].

Sandrini and colleagues reported that eletriptan 20 and 40 mg and placebo showed similar adverse-events rate (with a slight increase for the 40 mg), whereas the dose of 80 mg had a higher rate compared with the 40 mg dosage (1–7%) [Sandrini *et al.* 2009]. Also, the discontinuation rate due to the occurrence of adverse events was ranged from 0.2% (40 mg) to 1.6% (80 mg), and in other studies is reported as between 2% and 8% [McCormack *et al.* 2006; Almas *et al.* 2014]. The adverse-events frequency of eletriptan 20 and 40 mg is similar to that of supatriptan 50 and 100 mg, whereas the incidence with eletriptan 80 mg is slightly higher. Severe and serious adverse events are uncommon. The tolerability of eletriptan is also stable for long-term treatments and the incidence of adverse events may decrease over time [McCormack *et al.* 2006].

Among triptans, frovatriptan, rizatriptan, zolmitriptan, and eletriptan exhibit a higher frequency of central side effects possibly related to the presence of their active *N*-desmethyl metabolites. Although no data are available on the contribution of active metabolites of eletriptan to its tolerability profile, the higher lipophilicity of *N*-desmethyl eletriptan might be related to its ability to cross the blood–brain barrier. Together with the hypothesized higher brain concentration than the parent drug, *N*-desmethyl eletriptan might also be able to interact with 5-HT or other receptors associated with CNS side effects [Dodick and Martin, 2004].

Occurrence of serotonin-syndrome risk, when combining treatment with triptans and serotoninergic antidepressants has been reported by the

FDA. In a review of seven studies involving a large number of patients treated with eletriptan, with 306 patients coprescribed with serotoninergic antidepressants, no serious adverse events occurred [Tepper *et al.* 2003; Hettiarachchi and Kurrell, 2001]. Moreover, serotoninergic antidepressants might rarely precipitate serotonin syndrome when prescribed alone [Spigset, 1999]. Triptans and selective serotonin reuptake inhibitors (SSRIs) are frequently coprescribed because of the high comorbitity of migraine with anxiety and depression. The absence of a corresponding high number of serotoninergic-syndrome reports in the literature suggests that this adverse event is likely extremely rare [Tepper *et al.* 2003].

The FDA have assigned eletriptan to pregnancy category C (i.e. despite the absence of controlled data in human pregnancy, some previous studies carried out in animal models have shown evidence of toxicity with regard to the fetal development). Therefore, the prescription of eletriptan in pregnant migraineurs should only be considered in the absence of further alternatives [US Food and Drug Administration, 2013]. Furthermore, there is no previous information on increased risk of congenital malformations associated to triptan treatment during pregnancy, although the use of triptans during the second or third trimesters of pregnancy has been associated with a mild incremental increase in the risk of atonic uterus and hemorrhage [Nezvalová-Henriksen *et al.* 2010]. However, much lower eletriptan concentrations were detected in human breast milk when compared with maternal serum levels and, consequently, it is not likely to induce adverse effects in infants [Soldin *et al.* 2008].

Likewise, considering the eletriptan metabolism and the increase of CYP3A4 activity during pregnancy, modifications on the eletriptan efficacy profile should be also taken into account [Soldin *et al.* 2008].

Bio and drug interactions of clinical significance

The frequent prescription of a multiple-drug-therapy regimen for migraine, especially in its chronic form, increases the risk of occurrence of clinically significant drug–drug interactions (DDIs). In particular, patients treated chronically with the prophylactic therapy usually use triptans or other analgesics during an acute attack. The wide variety of both preventive and acute drugs and their possible pharmacological interactions complicates the choice of a combination therapy with a low rate of clinically significant DDIs [Lionetto *et al.* 2016].

Metabolism of eletriptan is primarily hepatic, with a main role of cytochrome P450 3A4 (CYP3A4). In patients with mild-to-moderate hepatic impairment treated with eletriptan, there is an increase in peak plasma concentration (C_{max}, 18%) and in the systemic exposure (AUC, 34%). Dosage adjustment in these patients might be not necessary. The use of eletriptan in patients with severe hepatic impairment has not been studied, therefore is not recommended [US Food and Drug Administration, 2013].

Given the most exclusive metabolism by CYP3A4, the eletriptan coprescription with drugs metabolized by the same cytochrome has been evaluated. In EU labeling, drugs contraindicated with eletriptan belong to the potent inhibitors of CYP 3A4 [inhibitory constant (Ki)] *in vitro* of 25 mol or less). Ketoconazole, itraconazole, erythromycin, clarithromycin, josamycin, ritonavir, nelfinavir, and indinavir are some of the CYP3A4 potent inhibitors [Thomas Healthcare, 2001]. Clinically significant pharmacokinetic interactions with eletriptan have been reported for several of these drugs, such as verapamil and fluconazole [Thomas Healthcare, 2001; Thummel and Wilkinson, 1998]. In the US, the intake of eletriptan before 72 hours from the treatment with a potent CYP3A4 inhibitor it is not recommended because of the risk of plasma concentration elevation. However, the frequency and severity of adverse events due to the co-administration of eletriptan and CYP3A4 inhibitors did not appear to be increased [Sandrini *et al.* 2009]. In a large study of patients treated with triptans, it was reported that, probably because of the wide variety of drugs metabolized by CYP3A4 [Thummel and Wilkinson, 1998], about half of the patients treated with triptans also received CYP 3A4-metabolized coprescriptions. In particular, one-fifth of the patients were coprescribed with potent CYP3A4 inhibitors and triptans, and 6% specifically with eletriptan [Tepper *et al.* 2003]. Growing clinician awareness of eletriptan means that concomitant prescriptions are not recommended, which might be useful in avoiding possible adverse events resulting from CYP3A4-based pharmacokinetic interactions.

No data have been reported about interactions causing any effect on the efficacy or undesired

effects of eletriptan and migraine prophylactic medications (beta-blockers, tricyclic antidepressants, SSRIs, methysergide and flunarizine). In clinical studies, administration of propranolol increased the exposure of eletriptan (AUC, 33%); but the effect is considered not clinically relevant since any increase in blood pressure or other adverse effects were associated with co-administration when compared with administration of eletriptan alone [US Food and Drug Administration, 2013]. Slight increases in blood pressure were observed with the intake of cafergot (caffeine and ergotamine) 1 and 2 hours after eletriptan, which is predictable considering the pharmacodynamics of the two drugs [Diener *et al.* 2002]. Therefore, ergot-type or ergotamine-containing medications (dihydroergotamine or methysergide) should not be administered within 24 hours after eletriptan dosing and *vice versa* [DrugBank, 2016]. Beta-blockers, tricyclic antidepressants, SSRIs, estrogen-based hormone-replacement therapy, estrogen-containing oral contraceptives and calcium-channel blockers have no effect on the pharmacokinetic parameters of eletriptan, as demonstrated by population pharmacokinetic analysis of clinical studies [Sandrini *et al.* 2009; Mathew *et al.* 2003a]. Moreover, monoamine oxidase (MAO) does not metabolize eletriptan and therefore has no expected interaction with MAO inhibitors [US Food and Drug Administration, 2013].

Conclusion

Triptan selection for each patient is a complex process that should take into account several clinical, pharmacological and individual variables. Among the pharmacological properties, eletriptan is a selective 5-HT_1 vasoconstrictive drug for the intracranial blood vessels compared with the other extracranial vessels, with a very low vasoconstrictive action on coronary arteries. Pharmacokinetic parameters are linear over the clinical-dose range, and eletriptan is primarily metabolized by hepatic cytochrome P450, accounting for the higher chance of bio and drug interactions. Eletriptan's clinical efficacy has been demonstrated in placebo-controlled and head-to-head studies. It showed the most favorable clinical responses among all triptans, together with sumatriptan subcutaneous injection, rizatriptan and zolmitriptan. It is a safe and tolerable drug, and is considered the triptan of choice in patients with cardiovascular risk factors, without coronary artery disease. Severe and serious adverse events are uncommon and the incidence of adverse events may decrease over time. Although there is hepatic metabolism by CYP3A4, any clinically relevant interaction has been demonstrated with the other first- and second-line prophylactic therapies or other acute treatments for migraine, with the exception of ergot derivatives and cafergot. Coprescription of eletriptan with drugs such as potent CYP3A4 inhibitors and other serotoninergic medications should be carefully considered.

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