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Tolerability of the Triptans
Clinical Implications

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Abstract

The triptans represent a relatively new class of compounds effective in the treatment of migraine. The safety and tolerability of these drugs have been extensively investigated since the first triptan (sumatriptan) became commercially available.

A report on a very large population of patients tested during clinical trials and in postmarketing studies, confirms that these drugs are safe and well tolerated when correctly used.

Adverse events are frequently reported, but are usually mild and only a few patients discontinue therapy because of them. These adverse events include, in particular, the so-called 'triptan symptoms' (tingling, sensation of warmth, etc.). The exact mechanism of chest symptoms reported by 20% of patients with migraine treated with triptans remains unclear, but are exceptionally related to a cardiac mechanism.

CNS adverse events (i.e. somnolence) are also reported, but it is a matter of debate whether they are related to the pharmacological properties (i.e. lipophilicity) of the drug or are symptoms of the disease itself.

The potential risk for drug overuse must be taken into account when the triptans are given to patients with a high frequency of migraine attacks.

Clinical interaction of triptans with other drugs metabolised in the liver may

theoretically influence the incidence of adverse events, but there is little evidence to support this assumption.

There is no evidence of a teratogenic risk of triptans in pregnant women taking these drugs.

The triptans are a new class of compounds known as serotonin (5-hydroxytryptamine [5-HT] receptor agonists).[1-4] The first of this family, sumatriptan, constituted a significant advance in migraine therapy,[5-10] and its development was quickly followed by a number of so called second-generation triptan compounds with improved pharmacokinetic properties, efficacy and/or tolerability profiles.

The triptans are believed to provide migraine relief by binding to serotonin receptors in the brain, where they induce vasoconstriction of extracerebral blood vessels and also reduce neurogenic inflammation.[3,4,11] Although the pharmacological mechanisms of the various triptans are similar, their pharmacokinetic properties differ.[3,12] These diverse pharmacokinetic properties could influence the effectiveness of the compounds and favour the prescription of one triptan over another in different patient populations.

Data from extensive clinical trials, coupled with information derived from widespread clinical use (nearly 10 years in the case of sumatriptan), indicate that the triptans are effective in the treatment of migraine attacks, generally well tolerated and, when used properly, have an acceptable benefit-risk ratio.[1-47] The clinical and pharmacological profile of the triptans has recently been reviewed in several articles.[1-5,11,12,19-31] The mechanisms and clinical implications of adverse events associated with the triptans are still being debated. A list of the main issues and specific problems concerning safety and tolerability of triptans is reported in table I.

1. Pathogenesis and Mechanism of Action of Antimigraine Drugs

Migraine can be defined as paroxysmal, recurring, moderate-to-severe attacks of unilateral throbbing headache exacerbated by physical activity and accompanied by features such as anorexia, nausea, vomiting, photophobia and phonophobia.[48-50] These accompanying symptoms can overlap with adverse events associated with antimigraine drugs making it difficult to distinguish between the former and the latter. Migraine is a common illness with a prevalence close to 10% in Western countries.[51-53] As such, it imposes an enormous health burden on both the patient and society. Lost work and productivity account for 80–89% of the economic burden of migraine.[53]

The mechanisms involved in the pathogenesis of migraine are still not fully understood. It has been suggested that alterations in the activity of serotonin-containing neurons in the raphe nuclei, and/or of noradrenaline (norepinephrine)-containing pathways originating from the locus coeruleus, result in depolarisation of trigeminovascular sensory afferents and the release of vasoactive neuropeptides (in particular, calcitonin gene-related peptide).[54-56] This activation produces a vasodilation of pial and dural arteries and exacerbates nociceptive transmission, leading to so-called sterile neurogenic inflammation.[57,58] This nociceptive impulse is transmitted, via orthodromic conduc-

Table I. Safety and tolerability of triptans: main issues and specific problems

Cardiovascular safety
Adverse events
Central effect
Chest pain symptoms
Serotonin syndrome
Correlation between adverse events and pharmacological profile
Triptans in pregnancy
Overuse
Clinical relevance of drug interactions

tion, to the CNS where it may induce migraine-associated symptoms.[54,59] Sensitisation phenomena seem to play a relevant role also.[60-63]

Many drugs used to treat migraine attacks, such as the ergots and triptans, are believed to have a vascular role. Triptans bind with high affinity to serotonin 5-$HT_{1B/1D}$ receptors, presynaptically on the trigeminal nerve that innervates these vessels, and centrally in the trigeminal complex of the brain stem.[55,64-72] The exact site of action of drugs for acute migraine, particularly 5-$HT_{1B/1D}$ agonists, has yet to be completely defined. Several studies indicate that the 5-$HT_{1B/1D}$ agonists have an effect on the CNS that might be relevant to their antimigraine action.[55,57] By contrast, several symptoms (e.g. malaise, fatigue, drowsiness, sedation, weakness) are characteristic features of the postmigraine period. These symptoms may be expressions of migraine relief rather than a direct drug-related effect.

The effect of the triptans on the trigeminal nucleus caudalis seems to be particularly important in their antimigraine activity. The fact that they improve not only headache, but also associated symptoms such as phono/photophobia and nausea/vomiting, the latter most probably via an action on receptors located within the brain stem, further support the suggestion that the antimigraine effect of triptans is in part centrally mediated.[11,55]

2. Adverse Effects of Triptans

In randomised controlled trials and in clinical practice, the triptans cause typical adverse events, which are referred to as 'triptan symptoms' or 'triptan sensations'.[4] The symptoms associated with the different triptans reportedly vary. They include, among others, tingling, numbness, a sensation of warmth, heaviness, and pressure or tightness in different parts of the body including the chest and neck, as well as symptoms more likely to be of CNS origin such as dizziness and sedation. In most cases these adverse events have been reported to be short-lived and mild to moderate,[4,18,73,74] but in long-term studies, adverse events have led to drug withdrawal in 6% and <10% of patients treated with sumatriptan 6 and 100mg, respectively,[8,75] and in 8% of patients treated with zolmitriptan 5mg.[76]

The highest incidence of adverse events (occurring in >50% of patients) was reported following the subcutaneous administration of sumatriptan 6mg [4,18] and included injection site reactions.[75] The site of injection is an important determinant for adverse events associated with subcutaneous administration of sumatriptan because of inadvertent intramuscular injection when using the auto-injector device.[77] In randomised controlled trials[4] the incidence of adverse events with other triptans (i.e. naratriptan, almotriptan) was comparable to that with placebo. The incidence of adverse events with sumatriptan (oral and subcutaneous) is reported in tables II and III.

The percentage of drop-outs from clinical trials or therapy because of triptan-related adverse events is relatively low. Some symptoms (chest symptoms in particular) can alarm patients, prompting them to interrupt treatment. Differences in sensitivity to triptans (as well as the varying efficacy and tolerability of the drugs in different patients) can be explained on the basis of individual predisposition. Thus, it is necessary to establish the lowest risk/benefit ratio in each individual patient.

Table II. Percentage incidence of adverse events in controlled trials of oral sumatriptan 100–300mg dispersible tablets for the acute treatment of migraine (reproduced from Brown et al.,[18] with permission)

Adverse event	Sumatriptan (n = 1456)	Placebo (n = 296)
Nausea/vomiting	14	7
Taste/disturbance	11	3
Malaise/fatigue	9	3
Dizziness/vertigo	6	2
Drowsiness	3	1
Heaviness	3	1
Weakness	3	<1
Chest symptoms[a]	3	<1
Throat symptoms	3	0
Neck pain/stiffness	3	0

a Principally tightness and pressure in the chest.

Table III. Percentage incidence of adverse events in controlled trials of subcutaneous sumatriptan 4–8mg for the acute treatment of migraine (reproduced from from Brown et al.,[18] with permission)

Adverse event	Sumatriptan (n = 1924)	Placebo (n = 868)
Injection site reaction	40	17
Nausea/vomiting	10	10
Tingling	9	3
Warm/hot sensations	9	3
Dizziness/vertigo	8	4
Heaviness	8	1
Pressure sensations	6	1
Flushing	6	2
Burning sensations	5	<1
Chest symptoms[a]	5	1
Neck pain/stiffness	3	<1
Tightness	3	<1
Weakness	2	<1
Headache	2	<1

a Principally tightness and pressure in the chest.

Despite extensive investigations into the efficacy and mechanism of action of the triptans, the factors involved in the induction of adverse events are still poorly understood. Possible mechanisms involved in some major adverse effects, such as chest symptoms associated with the administration of triptans, are discussed below.

3. Tolerability of Triptans

No migraine therapy has been studied as extensively and thoroughly as sumatriptan. From the beginning of the clinical trial programme for sumatriptan through to December 1998 (approximately 10 years), more than 88 000 patients with migraine received sumatriptan for more than 300 000 attacks of migraine and 2000 normal healthy volunteers were exposed to the drug. In addition, postmarketing and clinical practice data on sumatriptan, available in more than 80 countries, now extend to millions of patients with migraine.[78]

In all clinical trials, an adverse event was defined as any medical or clinical change that occurred or worsened after the administration of triptans and noted by the patients in diaries or reported to or observed by the clinician during the clinical trial.[20,22,79-81] In evaluating the safety of a product, it is often difficult to separate treatment-related events from coincidental events. The strategy, then, is to record all adverse events, including features of migraine itself (e.g. nausea, headache and postdromal symptoms), regardless of their suspected origin or cause. Using the controlled trials database, adverse event frequencies can be used to estimate spontaneous or coincidental adverse events.

Spontaneous reports of adverse events submitted during the extensive post-marketing use of sumatriptan provide a rich source of clinical practice data, which complement data derived from clinical trials and allow ongoing assessment of the drug's safety profile.[78] Disadvantages of using postmarketing experience rather than clinical trial information include incomplete and/or underreporting of adverse events, lack of control groups, and inability to follow-up the short- and long-term outcomes of adverse events.

However, data obtained postmarketing are important, since they concern a nonselected patient population treated in clinical practice. Serious adverse events following sumatriptan administration[78] are rare, and seem to be related mainly to the inappropriate use of the drug. The prescribing information on sumatriptan indicates that the drug should not be given to patients with a history, symptoms or signs of ischaemia, cardiac, cerebrovascular or peripheral vascular abnormalities. It is strongly recommended that sumatriptan is not given to patients who may, given the presence of certain risk factors such as hypertension, hypercholesterolaemia, smoking, diabetes mellitus and a strong family history of cardiovascular disease have unidentified coronary artery disease (unless a cardiovascular evaluation has provided satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischaemic myocardial disease or any other significant underlying cardiovascular disease). A progressive decrease in serious cardiovascular events in the pe-

riod 1992–1998[78] probably reflected increasingly careful selection of patients for treatment with sumatriptan, as well as class labelling restrictions imposed by regulatory authorities (i.e. US FDA). Exploratory studies in patients with a high risk of coronary artery disease revealed that triptans had a similar incidence of adverse events in these patients comparable to that found with placebo.[82] Studies in large populations are difficult to justify ethically.

Numerous specific studies have been carried out in controlled conditions in order to better evaluate the tolerability and safety of the triptans during long-term treatment. In this field also, sumatriptan, being the first triptan introduced on the market, is the drug most extensively investigated.

In long-term (1-year) studies in patients with migraine treated with sumatriptan, the adverse event profile was not changed or affected by attack frequency.[8] Patients treating >30 attacks of migraine with sumatriptan experienced fewer adverse events compared with patients who took sumatriptan for only a few episodes of migraine. This apparent decrease in the incidence of adverse events with more frequent use of triptans probably reflects not so much a true decrease in the incidence of adverse events as a lack of diligence on the part of the patient in reporting adverse events that cause them no concern.[8] The decrease in the incidence of adverse events was unlikely to be due to patient withdrawals because the overall withdrawal rate was extremely low and reflected the patients' view that the benefits of sumatriptan outweighed the risk of adverse events.[8] Furthermore, most patients who withdrew from the studies, because of adverse events, had treated <10 attacks of migraine with sumatriptan, which supported the view that no new tolerability problems occurred in the long-term and that patients who experienced adverse events after sumatriptan administration did so within the first few exposures. A similar pattern was observed in long-term studies of other triptans.[64]

Prospective large-scale studies were carried out in 12 339 patients with acute migraine treated with sumatriptan administered subcutaneously.[83] This type of investigation was mainly intended to give information on the safety of the drug, since the study design did not allow comparison of the tolerability of sumatriptan with that of other treatments for the acute management of migraine attacks. The adequacy of current labelling could be tested in this study, which confirmed a good safety record for this drug when used in accordance with labelling instructions.[83]

4. Comparative Evaluation of Tolerability

Tolerability is an important factor when choosing between drugs with apparently similar efficacy. Most studies are too small to accurately compare drugs for tolerability, even when the appropriate dose, dose frequency, and similar formulations have been used.

The reporting of adverse events has also been a problem.[20,22,79] Most studies quote the incidence of adverse events above a certain predetermined percentage; this varies from study to study (e.g. >3%, >5%, etc.). It is also difficult to establish uniform criteria for reporting adverse events. In some studies, adverse events are drawn from patient's diaries, while in other studies they are collected retrospectively.

While the definition of 'severe' adverse events is the same in all the studies (agreeing with the Good Clinical Practice and International Conference for Harmonisation Criteria[84,85] and including any condition in which the subjects dies, has a life-threatening event, is hospitalised or undergoes prolonged hospitalisation, etc.), the conditions in which nonsevere adverse events may occur can be difficult to define.

The use of different criteria, subjective evaluation of adverse events by the patient and subjective judgement of adverse events by the investigator can introduce a major bias and reduce the value of drug tolerability comparisons between trials. Another critical point concerns the adverse event

glossary; in most of the trials it is not used and the same symptom can be classified under different adverse event groups thereby reducing the event's true incidence. Direct active comparator trials have been conducted with reference to only a few triptans.[81] Although studies of this kind have been deemed the gold standard for comparing drugs, they can present considerable problems, which complicate their interpretation. However, the triptan trials are very similar in terms of study methods and populations, facilitating meta-analysis of the different studies to summarise the efficacy and tolerability of the different triptans.[20,80]

To compare the tolerability of the different triptans several parameters have been suggested: overall incidence of adverse events (the percentage of patients who, having taken the drug, experience an unexpected or undesired event including all adverse events not just drug-related); the number needed to harm (NNH), i.e. the average number of patients treating one attack needed in order to encounter one adverse event (with this parameter, the greater the number the better the tolerability);[80] and therapeutic penalty (the NNH is the reciprocal of the therapeutic penalty when expressed as a proportion).[80]

Another interesting approach is to consider the placebo subtracted adverse event data.[20] Moreover, since the clinical relevance of the adverse event related to triptan intake can vary, it has been suggested that adverse events be divided into three main groups including any adverse event, adverse events of CNS origin, and adverse events pertaining to the chest.[20]

An interesting article was published evaluating 53 clinical trials (12 unpublished) involving 24 089 patients using oral triptans for acute migraine.[20] This study concerned both triptans already in the market and those to be introduced into the market shortly (sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan). The main adverse event data reported in this study are shown in figure 1.

The author's commented that 'differences in total adverse event rates must be interpreted cautiously since they reflected proportions of patients with at least one adverse event irrespective of their number, nature, or intensity; trivial and significant adverse events were thus pooled. In addition, in the almotriptan studies, adverse event rates for placebo and sumatriptan are remarkably low. This finding could indicate different methods of collecting and defining adverse events, a study population with a higher threshold for reporting adverse events, or both'.[20] Specific comparative trials should aim to define the profile of efficacy and tolerability of the second-generation triptans.

5. Chest Symptoms

Typically, $5HT_{1B/1D}$ agonist-induced symptoms are tightness, heaviness, pressure, and/or pain in the chest, neck, and/or throat.[4,86] The pathophysiology of these chest symptoms, which are a cause for concern because they occasionally mimic angina pectoris,[86-88] remains to be determined.

In clinical practice, between 20 and 40% of patients treated with sumatriptan administered by tablet or subcutaneous injection, respectively, experience tightness, heaviness and/or pressure in the chest, neck or throat. The percentage of patients reporting chest symptoms is lower in clinical trials than in clinical practice (approximately 5% for sumatriptan). Percentages of chest symptoms equal to that observed after placebo administration was reported in some second-generation triptan trials, i.e. almotriptan.[40]

Dahlof and Mathew investigated the possible existence of factors increasing the migraine patient's risk of experiencing chest symptoms. Pressure sensations in the chest, neck, or throat were observed in 15–40% of patients after administration of sumatriptan.[86] The majority are young to middle-aged women who generally have a lower incidence of cardiovascular risk factors. In a retrospective survey, it was likewise demonstrated that chest symptoms were experienced more frequently by women than by men, in younger rather than older patients, and by those with a low rather than high body mass index.[86,87] In the group of patients that used sumatriptan tablets, smoking tended to be

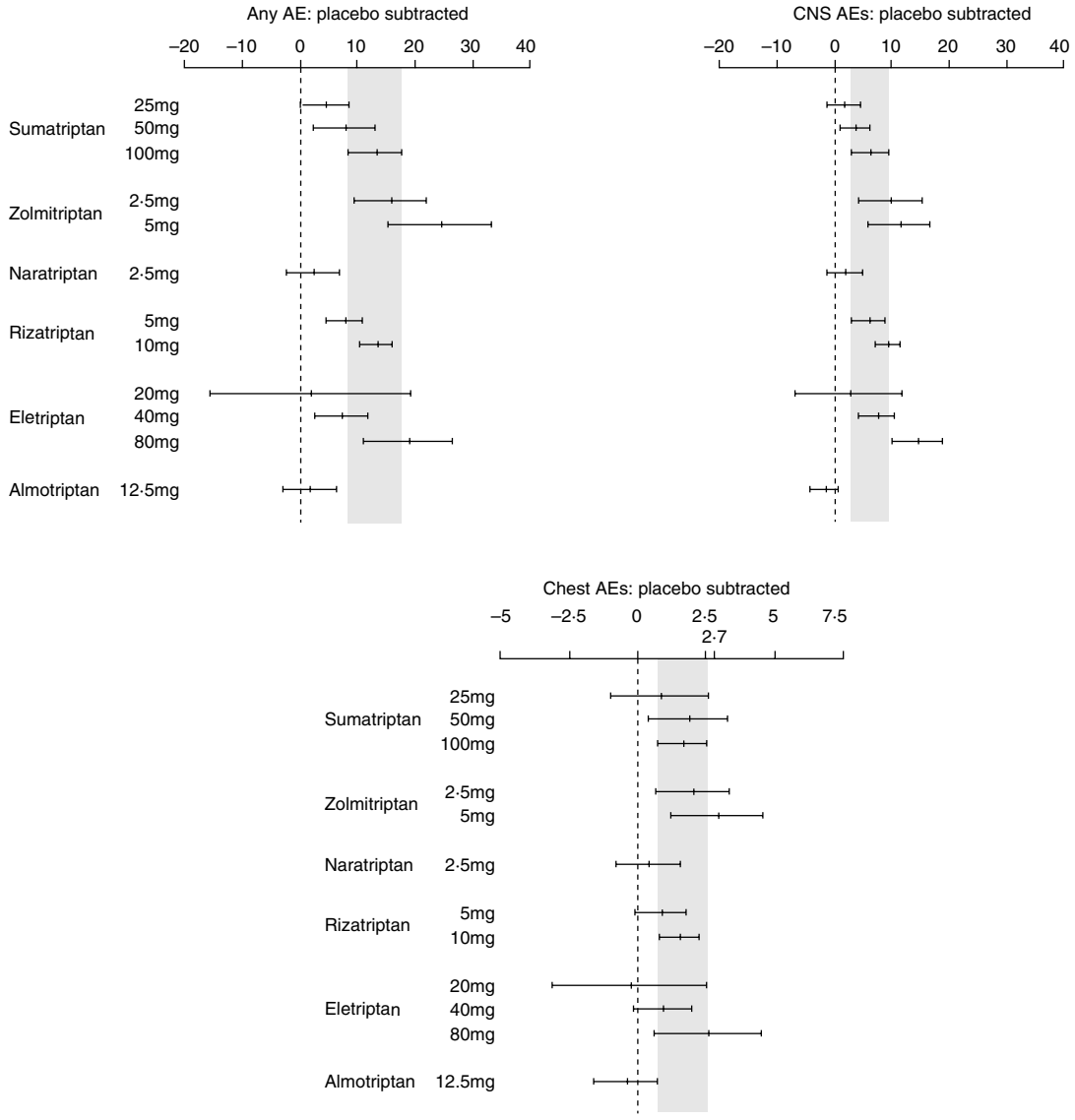

Fig. 1. Placebo subtracted adverse event (AE) data in a meta-analysis evaluation of 24 089 patients with acute migraine treated with oral triptans. Mean and 95% CI given for each triptan. Grey shaded area is the 95% CI for sumatriptan 100mg (reproduced from Ferrari et al.,[20] reprinted with permission from Elsevier Science [*The Lancet* 2001; 358: 1673]).

associated with an increased risk of sumatriptan-induced chest symptoms.[88]

Several explanations have been put forward to explain the mechanism of adverse symptoms associated with sumatriptan use.[89-95] The unpleasant symptoms of pressure/tightness over the chest and pressure/stiffness in the throat and neck probably have a similar aetiology.[86,87] Dahloff and Mathew[86] concluded that chest and throat symptoms should not be misinterpreted as being of

cardiac origin, and that true cardiac ischaemia in association with the use of 5-$HT_{1B/1D}$ agonists appears to be rare in migraine sufferers. Alternative mechanisms of action of 5-$HT_{1B/1D}$ agonists support the notion that the chest/throat symptoms encountered are not of cardiovascular origin.

6. Cardiovascular Safety

According to the vascular hypothesis of migraine, the therapeutic efficacy of sumatriptan is primarily related to its agonist activity at the level of 5-$HT_{1B/1D}$ receptors, which mediate constriction of carotid arteriovenous anastomoses and intracranial cerebral blood vessels.[1,3,4] However, despite the fact that the drug is highly effective in alleviating migraine attacks, sumatriptan is contraindicated in patients with coronary artery disease since, as demonstrated in experiments conducted both *in vitro* (H6) and *in vivo*, 5-$HT_{1B/1D}$ receptors are also abundant in coronary artery vessels.

It has been shown that sumatriptan constricts the isolated human temporal artery via 5-HT_{1B} but not 5-HT_{1D} receptors. In the human coronary artery, 5-HT_2 receptors are more important, but about 20–30% of the constrictor response is mediated by 5-HT_1 receptors.[96-111] Figure 2 (lower panel)[104,105] shows the ratio between the unbound maximum plasma concentration (C_{max}) after administration of clinically effective doses of triptans and the concentration of the different compounds in the human isolated coronary artery required to obtain 50% of the maximal contractile response (EC_{50}). A C_{max}/EC_{50} ratio of 1 indicates that the drug (active metabolite excluded, see Maassen Van Den Brink et al.[104]) would elicit 50% of its maximum contraction in a clinical situation. Because, in each case, the C_{max}/EC_{50} ratio is well below 0.4 (and even below 0.05 in the case of zolmtriptan and eletriptan), the triptans are expected to cause little coronary artery disease (stenosis or hyper-reactivity), while the second-generation triptans may still cause myocardial ischaemia.[4,104]

In an attempt to obtain safer triptans (i.e. those that are more cerebral vessel than coronary artery selective[71,106,107]) newer triptans (the so called second-generation triptans) have also been developed. *In vitro* and *in vivo* experimental studies indicate that some of the newer triptans are more selective than sumatriptan in their action on the cerebral vessel. In the case of eletriptan, administered at a dosage similar to that used in clinical practice, an absence of vasoconstrictor effect on coronary vessels was documented in a few cases during coronarography.[99]

It remains difficult to determine the clinical implications of these clinical and experimental studies, and use of the newer triptans are also absolutely contraindicated in patients with suspected cardiac ischaemia or angina.

The chest symptoms may be a consequence of coronary vasoconstriction and cardiac ischaemia; 5-$HT_{1B/1D}$ agonists constrict human coronary vessels *in vitro* to a lesser extent (20–30% of the constriction is produced via 5-HT_2 receptors and noradrenaline [via α-receptors]).[88,110,111] Serious cardiac events have been reported after administration of the 5-$HT_{1B/1D}$ agonist sumatriptan and a causal relationship between its use and rare cardiovascular ischaemic events or deaths cannot be excluded.[112-117] The contraindications, according to the official data sheet for the use of the 5-$HT_{1B/1D}$ agonist sumatriptan, are cardiovascular and arterial diseases such as angina pectoris, arteriosclerosis, uncontrolled hypertension, and Raynaud's disease.

Considering the extensive use of sumatriptan, the incidence of serious cardiac adverse events is low.[78] In view of the ECG and ECG Holter data gathered during avitriptan administration, the cause of chest symptoms clearly remains to be determined, although nonpathological ECG changes have been seen in a large patient series during the first hours after treatment.[118]

In the majority of migraine patients, 5-$HT_{1B/1D}$ agonists may be considered safe, especially in women without cardiovascular risk factors. Serious hypersensitivity could also play some role.[86]

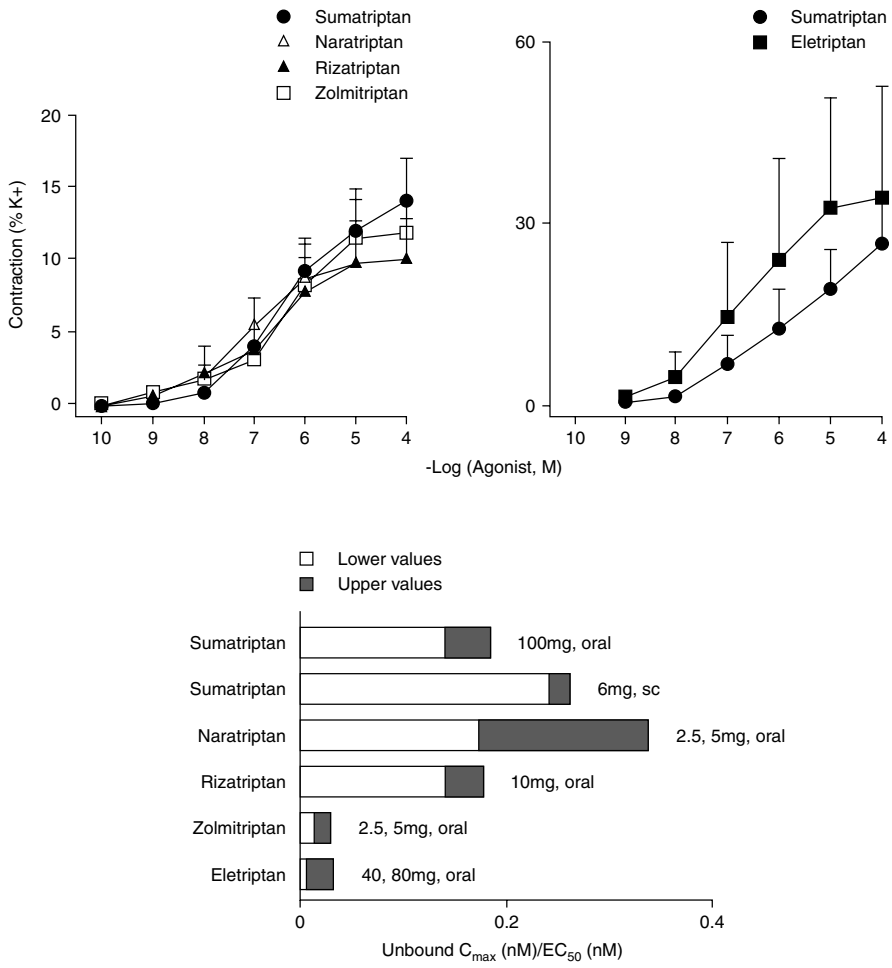

Fig. 2. Coronary effects of triptans. Upper panels: Concentration-response (expressed as percentage of responses to 100mM K+) curves in human isolated coronary arteries obtained with sumatriptan, naratriptan, rizatriptan, and zolmitriptan (n = 9, upper left panel; data taken from Maassen Van Den Brink et al.,[104]) and sumatriptan and eletriptan (n = 9, upper right panel; data from Maassen Van Den Brink et al.,[105]). Lower panel: Relationship between reported C_{max} concentration (corrected for plasma protein binding) in patients and EC_{50} values in the contracting human isolated coronary artery. Frovatriptan, which also constricts the human coronary artery (Parsons et al.,[100]), has not been included because the exact therapeutic dose and plasma protein binding level were not known (reproduced from Saxena and Tfelt-Hansen,[4] with permission from Lippincott Williams and Wilkins, Philadelphia, 2000). **C_{max}** = maximum plasma concentration; **EC_{50}** = 50% of the maximum contractile response; **sc** = subcutaneous.

7. Triptans in Pregnancy

While migraine often improves during pregnancy, it also sometimes occurs for the first time during pregnancy, and may worsen during the first trimester.[119-121] In clinical trials of experimental drugs, the likelihood of a woman becoming pregnant while taking a given drug is very much reduced. When a product is marketed, spontaneous reports of prenatal exposures are received through

the adverse event reporting system and are reviewed for safety signals. Reports of birth defects are carefully evaluated to establish a possible relationship with the drug, and drug regulatory agencies are informed.

Recently, data were published on pregnancy outcomes following prenatal drug exposure, in particular sumatriptan.[122-126] The present estimate of the teratogenic risk associated with migraine drugs, and especially sumatriptan, is reassuring for the individual woman who uses this drug. The estimated rate of congenital malformations (2.7%) is even lower than the overall population risk (3.6%). The hypothetical risk of an undetected teratogenicity for a specific malformation must be weighed up against the therapeutic benefit to the patient. Current data do not support a need to interrupt pregnancy following embryonic exposure to sumatriptan.[122-125]

Some authors found that sumatriptan exposure during pregnancy was associated with an increased risk of preterm delivery and low birth weight.[122] These findings may be due to drug exposure, but they may also be attributable to the severity of the disease itself, rather than the treatment or confounding factors or chance.

8. Overuse and Daily Use of Triptans

The triptans are effective as treatment for acute migraine, and recently a possible prophylactic use of these substances has also been proposed. Naratriptan was found to be an effective short-term prophylactic treatment for migraine associated with menstruation in a double-blind study versus placebo.[127] The tolerability of naratriptan was similar to that of placebo.[127] A remarkable reduction in the frequency and intensity of daily headache was observed when naratriptan was used in the prophylaxis of transformed migraine. However, the study in question included only a few patients even though the drug was well tolerated by the three patients treated with naratriptan.

Several reports of drug-induced headache following frequent use of triptan have been published[128-132] and the possibility of medication overuse needs to be considered in migraine patients who have a high attack frequency and who take triptans. Interestingly, withdrawal headache is shorter and less severe in migraineurs overusing triptans than in those overusing ergots or analgesics[128] and in patients receiving nonsteroidal anti-inflammatory drugs. Furthermore, the triptans have a better prognosis as regards the risk of relapse.[128] There is no evidence concerning the possible risk of increased adverse events in daily users of triptans for cluster headache.[130,131] Moreover, no relationship between headache recurrence and triptan overuse has been documented.[133-135]

9. CNS Adverse Events

The mechanisms involved in pathogenesis of CNS adverse events following the administration of triptan are not clear. So-called 'central adverse events' (i.e. somnolence, dizziness, etc.) feature frequently among the adverse effects reported by patients with migraine after triptan therapy. Since several of these effects could overlap with symptoms typically occurring during a migraine attack, it can be difficult to evaluate the real incidence of central CNS-associated adverse events.

Lipophilic drugs (of any therapeutic class) tend to cause adverse events involving the CNS. For example, dizziness, somnolence, and drowsiness are characteristic adverse events that distinguish the more lipophilic tricyclic antidepressant agents and β-adrenoceptor antagonists (β-blockers) from hydrophilic agents of the same therapeutic classes.

In a study on comparative tolerability of oral 5-$HT_{1B/1D}$ agonists,[136] the frequency of adverse events could not be predicted from *in vitro* measures of lipophilicity, *in vivo* estimates of absolute bioavailability, drug dose, or any combinations of these variables.

In a study investigating the pharmacokinetics of zolmitriptan, the drug induced a dose-related increase in CNS adverse events (e.g. somnolence) [137] suggesting that this effect was dependent on specific pharmacological properties of the drug.

It has been suggested that the activity of P-glycoprotein inhibitors (including eletriptan) could in-

duce adverse CNS events. However, this suggestion is currently debated as there is no evidence that these drugs, at therapeutic doses, reach blood levels high enough to produce clinically significant P-glycoprotein inhibition.[138-140] Moreover, no clear correlation between serotonin receptor subtypes (i.e. $5HT_B$, $5HT_D$, $5HT_F$, etc.) and CNS adverse events has been established.[1-3]

It has recently been suggested that triptans with enhanced lipophilicity (i.e. naratriptan and zolmitriptan) may reduce central serotonin levels, potentially exacerbating depressive illness, but no increased rate of referrals for depressive illness emerged when comparing the newer triptans with sumatriptan, which acts predominantly as a peripheral 5-$HT_{1B/1D}$ agonist.[141]

10. Drug Interactions

All triptans are metabolised in the liver.[2,21] Sumatriptan is metabolised by monoamine oxidase-A (MAO-A), which is found in the liver and gastrointestinal tract. Naratriptan is metabolised by cytochrome P450 (CYP) enzymes and its clearance is reduced by oral contraceptive use and increased by smoking.[138] The metabolism of zolmitriptan involves both CYP1A2 isoenzyme and MAO-A. Zolmitriptan is metabolised to an active N-desmethyl metabolite, which is two to six times more potent than the parent compound, a factor that may contribute to its overall efficacy. Rizatriptan is primarily metabolised by MAO-A to inactive metabolites and an active N-monodesmethyl metabolite (with activity similar to that of the parent compound). Interaction with other cytochromes, such as CYP3A4, have been reported with triptans such as eletriptan).

Several studies have been carried out in order to explore interaction between triptans and drugs interacting with MAO-A, CYP and serotonin receptors.[142-145]

The majority of these studies were designed to evaluate pharmacokinetic interaction rather than to assess the clinical effect on tolerability.

The main pharmacological interaction between the triptans and MAO inhibitors, ergot-containing drugs, serotoninergic drugs (i.e. selective serotonin reuptake inhibitors), β-blockers and cimetidine was recently reviewed by Gawel et al.[21]

The possibility that triptans induce a serotonin syndrome when administered concomitantly with serotoninergic drugs needs to be considered, as does the possibility of additive vasospastic reaction during treatment with ergot-containing drugs or their derivates.

The exact mechanism involved in the precipitation of the serotonin syndrome is not well known, but central action and neuroendocrinological effects of triptans could play an important role.

Pharmacological evidence that α-adrenoreceptors mediate vasoconstriction of carotid arteriovenous anastomoses[146] in animals could constitute an indication that the association between the triptans and drugs interacting with these receptors is clinically dangerous in some conditions, even though no clear evidence is as yet available to support this hypothesis.

Since drug interactions vary for each triptan, it is necessary to evaluate them carefully before making a therapeutic choice.

11. Conclusions

The triptans, well recognised as effective symptomatic medication for acute migraine attacks, are safe when used appropriately. The profile of tolerability is good and is similar to that observed after placebo administration in some clinical trials.

There are no criteria as yet that allow establishment of individual susceptibility to adverse events after triptan administration. A better understanding of the mechanism(s) underlying triptan-induced adverse events, as well as genetic factors involved in susceptibility to migraine could encourage a better and more personalised use of the triptans in migraine patients.

The level of knowledge related to triptans (i.e. pharmacological profile, efficacy, tolerability) can be considered very high. Despite publication of data in relevant scientific journals some individuals consider that, seen as most of these articles are supported by pharmaceutical companies, they tend

to overestimate the positive aspects and to minimise the negative effects of the drugs. Therefore labelling information, as approved by regulatory authorities, has to be carefully considered.

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