

## Of the available triptans, which should be chosen and how should they be used?

Dos triptanos disponíveis, quais devem ser escolhidos e como devem ser usados?

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### ABSTRACT

There is a plethora of articles dealing with the use of triptans to treat migraine, but so far no unanimity exists regarding the optimal form of using this group of drugs in a patient with recurrent attacks of migraine. Although all of them may exert their pharmacological effects through a known specific mechanism of action, i.e. agonist effects on serotonin 5-HT (1B/1D) receptors, distinct differences exist. The author comment a few facts on the prescription of triptans and possible adverse effects, depending on the clinical scenario. Thus, even though an enormous amount of information has accumulated over the last few decades on triptans, several questions remain to be answered, and research priorities need to be addressed.

**Keywords:** Triptans, Adverse Effect, Migraine, Prescription.

### RESUMO

Há uma infinidade de artigos que tratam do uso de triptanos no tratamento da enxaqueca, mas até agora não existe unanimidade em relação à forma ideal de usar esse grupo de medicamentos em um paciente com ataques recorrentes de enxaqueca. Embora todos eles possam exercer seus efeitos farmacológicos através de um mecanismo de ação específico conhecido, isto é, efeitos agonistas nos receptores da serotonina 5-HT (1B/1D), existem diferenças distintas. Os autores comentam alguns fatos sobre a prescrição de triptanos e possíveis efeitos adversos, dependendo do cenário clínico. Assim, embora uma quantidade enorme de informações tenha se acumulado nas últimas décadas sobre triptanos, várias questões ainda precisam ser respondidas e as prioridades de pesquisa precisam ser abordadas.

**Descritores:** Triptanos, Efeito Adverso, Enxaqueca, Prescrição.

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There is a plethora of articles dealing with the use of triptans to treat migraine, but so far no unanimity exists regarding the optimal form of using this group of drugs in a patient with recurrent attacks of migraine. Although all of them may exert their pharmacological effects through a known specific mechanism of action, i.e. agonist effects on serotonin 5-HT (1B/1D) receptors, distinct differences exist.

Rapoport and coworkers<sup>1</sup> suggested a few strategies to be adopted when choosing a triptan. They pointed out that some patients prefer a form of treatment that works quickly, some consider as satisfactory treatment triptans that provide complete relief of the pain, while others expect consistent effects as the most important result of triptan treatment. In addition, adverse effects are not tolerated by some migraineurs.<sup>1,2</sup>

Almas and colleagues<sup>3</sup> reported that eletriptan provides consistent migraine relief with an 80-mg dose. Some of these individuals reported failure with a lower dose of 40 mg. This is of major importance since the failure of triptan treatment may be caused by the use of subtherapeutic doses. However, 80 mg is the maximum daily dose allowed and a subsequent intake of eletriptan must be avoided to prevent serious adverse effects. Nevertheless, only 18.6% and 8% of the patients achieved pain-free status at 2 hours or 24 hours sustained headache response, respectively, on all three sequential treated attacks.<sup>3</sup> Although this is an excellent clinical outcome in terms of current treatment of migraine attacks, it is far from the ideal goal of a foreseeable 100% effective antimigrainous drug.

Seven triptans are currently being used in clinical practice (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan)<sup>1,2</sup>. The relevant literature is controversial regarding the most successful triptan in the treatment of migraine attacks. A number of specific advantages are claimed for some of them as compared with the others. Thus, among the available triptans, which one should be chosen to treat a given patient is still a moot point. In part, this is also due to the different ways in which triptans are tested for their efficacy and possible adverse effects.

Different study end-points are evaluated during trials using triptans.<sup>4</sup> Even though an attempt is always made to attenuate bias during clinical trials, it is virtually impossible to eliminate completely. The 'negative result' bias and the supposed influence of pharmaceutical companies over the publication of favorable results of a given drug produced by them must be considered when interpreting study outcomes.

Huge amounts of money have been spent by pharmaceutical companies to develop new drugs, and the companies' efforts in this regard should be recognized. As a result, we have acquired a very high level of understanding of the mechanisms of action of triptans and their possible clinical applications.

Regarding the clinical use of triptans for migraine attacks, a long-action triptan is the ideal treatment for patients with crises of headache lasting over six hours. Among the triptans naratriptan (5-6 hours) and frovatriptan (26 hours) present a relatively long half-life,

and should therefore be remembered when prescribing for such patients.<sup>2</sup> If a short-action triptan is to be used, the physician may recommend an abortive dose of the triptan in addition to a complementary "prophylactic" dose a few hours later, and before the expected recurrence of the headache, in order to maintain the patient free of headache, bearing in mind the maximum safety dose of the drug that one may use daily. This form of treating (abortive/preventive) is not usual in clinical practice. Some authors use the combination of a triptan and NSAIDs to treat such migraine attacks.

The efficacy of a specific triptan does not always correlate with the patient's preferred treatment. The choice of a triptan by the physician will depend upon his or her previous experience, the brand name, marketing pressure, the usual features of the migraine attacks, drug availability, cost, possible adverse side effects, the patient's risk of concomitant atheromatosis, vasospasm susceptibility, or a previous failure or side effect with a particular triptan reported by the patient.

The consensus is that triptan treatment in migraineurs does not increase the risk of stroke, cardiovascular death, or ischemic heart disease.<sup>5</sup> The contraindications for the use of triptans are still poorly defined. There is general agreement that triptans should not be used by patients with a previous stroke or cardiovascular events. However, we should be concerned when dealing with patients with more than two of the following risk factors for atheromatous disease: age >55 years, smoking, arterial hypertension, dyslipidemia, diabetes mellitus or a familial history of myocardial infarction at a young age. Migraine with aura by itself seems to be a risk factor for ischemic cardiovascular disease in women, and the widespread use of hormonal contraception further enhances this risk.

Considering the potential vasoconstriction of the coronary artery elicited by triptans as *in vitro* studies have shown, the number of cardiovascular adverse events reported is surprisingly low.<sup>5</sup> I wonder whether this is a consequence of the characteristic behavior of the migraineurs in avoiding intense physical activities or to the attempt to remain at rest during a migraine attack.

Considering the abovementioned risk factors, we still do not know if there is a significant risk of symptomatic vasoconstriction if we treat an athlete performing a sporting activity with triptan. This scenario must be relatively frequent since the current recommendation is an early treatment of a migraine attack when the pain is still mild.<sup>6,7</sup> In this line of thinking, should one be afraid of an ischemic event if during an exercise a person presents "triptan sensations" (*i.e.* chest, jaw or arm discomfort)?<sup>8</sup> This question remains to be answered.

As future research priorities we should address the following questions: Why do some patients not respond to triptan? What are the clinical and demographic characteristics of patients who respond, compared to nonresponders<sup>9</sup>? By answering this, we can, therefore, identify those less likely to respond to triptan before prescribing this particular pharmacological agent. Could rest or sleep in a dark room potentiate the action of a triptan compared to subjects that continue their daily activities? Do some environmental conditions (light/

darkness, noise, weather), physiological events or mental states (sleep, anxiety, stress, fear, hunger) influence the action of the drug on the specific migraine attack treated with triptan? It seems that this may be so, which would account for the absence of consistency observed with the use of triptans used at the same dose at different times and by the same individual.

Could variables such as age and gender influence the response to triptans? Why do some patients respond to a specific triptan after reporting a failure of response to a different triptan? Pharmacogenetics may explain this at some future date.

One topic to be discussed is the use of triptans by sexually active women during their fertile period. Although triptans should be avoided during pregnancy, women may use this drug in the first month before realizing that they are pregnant. Does this increase the chance of a possible teratogenic effect of the drug compared to other classes of analgesics? Evidence has suggested that the use of triptans during pregnancy is associated with atonic uterus and blood loss during labor, but the risk of major birth defects is comparable to that of the general population.<sup>10</sup>

Another important issue is whether the physician should explain the contraindications of triptans to the patient. Some may argue that this is not necessary for young patients with no cardiovascular risks. However, it is not uncommon for patients to recommend a painkiller to colleagues and family members, so they need to be made aware that triptans may have serious adverse effects when taken inappropriately. Furthermore, a patient may use triptans for decades without returning to the prescribing physician and his or her safety profile may change with age. This is another point to be borne in mind, considering the importance of patient education.

Thus, despite the fact that an enormous amount of information has accumulated over the last few decades

on triptans, several questions still remain to be answered and research priorities need to be addressed.

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