Triptans (serotonin, 5-$HT_{1B/1D}$ agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials.

Cephalalgia 2002 April 11, 22: 633-658

Triptans are well-known and widely used medications in the abortive treatment of migraine. They are agonists of 5-$HT_{1B/1D}$, which work via cranial vasoconstriction, peripheral neuronal inhibition, and inhibition of transmission through second order neurons of the trigeminocervical complex. The most commonly prescribed dose and first available option for triptan use was Sumatriptan 100 mg daily. However, at the time of this study, there were 7 different triptans (sumatriptan, rizatriptan, eletriptan, naratriptan, zolmitriptan, frovatriptan, and almotriptan) for clinicians to choose from. For this reason, this meta-analysis was conducted in order to compare the various triptan options for more clarity in triptan choice. Although many formulations exist, the oral option is often preferred by patients and accounted for >80% of all prescriptions, thus this study focused only on oral formulations. Of note, all triptans are contraindicated in the presence of cardiovascular disease.

Experimental design: This study was a meta-analysis of complete data sets of all eligible clinical trials related to triptan use. The authors requested all "raw patient data" of all randomized control studies involving each of the triptans. Frovatriptan was the only medication and company (Vanguard) to decline, so only public data was utilized. They also conducted a systematic review of all available, though not company sponsored data, as well.
Inclusion criteria was as follows:

1. Randomized, double blinded control (placebo or active competitor) clinical trial
2. Treatment of moderate/severe attack within 8hrs in adult migraineurs (per ICHD criteria)
3. Treatment with oral triptan at recommended dose
4. Measurement of headache on a 4-point, pain scale

A total of 53 trials were included with common exclusions made for lack of control group, use of non-recommended doses and selected study population. Differences in all endpoints were compared using the random effects model. To control for differences in methodology, 4 different methods were used, including a rate ratio, therapeutic gain, NNT, and comparisons of absolute values –all yielded similar results.

Results*:* Regarding drug metabolism, the longest half-lives were seen in frovatriptan, naratriptan, and eletriptan, though the authors note that this may not guarantee longer periods of efficacy. T_{max} (time to peak plasma levels) was shortest in Rizatriptan (1 hour), but is only relevant if time to peak level occurs during an attack. Notably, some drugs also had double peaks, further complicating the interpretation of this data. Triptans with higher oral availability were almotriptan and naratriptan.

All results were also compared to Sumatriptan 100 mg, as this was the most commonly prescribed dose and first available option on the market. Comparisons were as follows:

1) Headache response at 2 hrs (most common primary end point):
   - Higher response rates in Rizatripatn 10mg and Eletriptan 80mg
   - Lower response rates in Naratriptan 2.5mg, Eletriptan 20mg, and Frovatriptan 2.5mg

2) Pain-free at 2 hrs:
   - Higher pain-free rates: Eletriptan 80mg, Almotriptan 12.5mg, and Rizatriptan 10mg
   - Lower pain-free rates: Sumatriptan 25mg, Naratriptan 2.5mg, and Eletriptan 20mg

3) Recurrence:
   - Higher recurrence rates: Rizatriptan 5mg and 10mg
   - Lower recurrence rates: Eletriptan 40mg and 80mg

4) Sustained Pain-Free Period:
   - Higher pain-free rates: Rizatriptan 10mg, Eletriptan 80mg and Almotriptan 12.5mg
   - Lower pain-free rates: Eletriptan 20mg

5) Intra-patient Consistency (efficacy over multiple attacks):
   - 1 out of 3 actively treated attacks aborted: 79-89%
   - 2 out of 3 actively treated attacks aborted: 47-72% (highest consistency in Sumatriptan 100mg and Almotriptan 12.5mg)
   - 3 out of 3 actively treated attacks aborted: 16-47% (highest consistency in Sumatriptan 100mg and Almotriptan 12.5mg)

Side effects were common with triptans, though mild and including tingling, paresthesia, and warm sensation in the head, neck, chest and limbs. CNS adverse effects, such as agitation, ataxia, confusion, tremor, vertigo, were more commonly seen in Eletriptan and less commonly seen Almotriptan. Chest adverse effects (chest pressure, pain, palpitations) had the lowest incidence in Almotriptan. These results should be interpreted with some level of caution, given that studies varied on how side effects were reported.

Conclusion*:* As compared to Sumatriptan 100mg, Rizatriptan 10mg seems to offer better efficacy and consistency and similar tolerability. Eletriptan 80mg offers better efficacy, similar consistency, but lower tolerability. Almotriptan 12.5mg offers better sustained pain-free period, consistency and tolerability while similar efficacy. Overall, this trial allowed us to compare the various triptans available, and it allowed clinicians to choose the most appropriate medication for their patients based on their specific migraine profile.

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