Editorial

Adding NSAIDs to triptans: Could less be more?

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Used as monotherapy, triptans and nonsteroidal anti-inflammatory drugs (NSAIDs) work well to treat individual attacks of migraine. Both are first-line treatment choices for patients who have episodic headaches and no contraindications to their use. They are not effective for all patients, however, and for others they provide only unreliable or incomplete relief. A substantial body of evidence supports the strongly held clinical belief that triptans work best when an optimal dose is given parenterally while pain is mild or moderate. One expert has observed that “most patients respond to triptans if the right drug and the right formulation are used” (1). Still, even 10 mg of naratriptan given parenterally—a dose and formulation that are not clinically available—results in elimination of headache pain two hours after treatment for only 88% of patients (1).

This shortfall in treatment success meant that as soon as the triptans entered clinical use, patients and doctors began to try them in combination with other drugs in an effort to obtain synergistic results. The combination of triptans and NSAIDs makes particular sense because the two drug classes have different adverse event profiles and mechanisms of action. In 2008 the United States Food and Drug Administration approved a fixed-dose combination tablet containing 85 mg of sumatriptan and 500 mg of naproxen sodium. The approval was based on clinical trial results showing that the combination worked better than placebo or either drug alone (2).

In this issue of Cephalalgia, Tullo and colleagues report results of a study that evaluated a combination of a different triptan/NSAID pair: frovatriptan with dexketoprofen (3). Frovatriptan has an elimination half-life of roughly 25 hours, in comparison with about two hours for sumatriptan, while dexketoprofen is an NSAID with a relatively short half-life and rapid onset of action (4,5). The investigators hypothesized that dexketoprofen would provide good early relief of migraine pain while the longer half-life of frovatriptan would reduce headache recurrence, defined as “a headache of any severity returning within 48 hours, in a subject who was pain free at two hours and who had not taken rescue treatment.”

The study tested 2.5 mg of frovatriptan in combination with 25 mg or 37.5 mg of dexketoprofen, against the combination of 2.5 mg of frovatriptan with placebo. This made it possible to assess not only whether the combination of frovatriptan and dexketoprofen was superior to frovatriptan alone, but also whether a higher dose of an NSAID was better than a lower dose. When results from the 279/314 participants with evaluable data were analyzed, the researchers found that both frovatriptan/dexketoprofen combinations were statistically significantly more effective than frovatriptan alone for outcomes of pain-free status at two hours and sustained pain-free status at 24 and 48 hours. Time to pain relief was statistically significantly improved with the combination compared with frovatriptan alone, although headache recurrence with the combination was not different.

An unexpected finding, though, was that the combination with the higher 37.5 mg dose of dexketoprofen showed no clear advantage over that with the lower dose of 25 mg (3). The lack of a dose-response relationship was seen across a variety of study end points, which increases confidence that it is not a chance finding. This is surprising because, at least when used as standalone treatments, previous research suggests that there is a dose-response relationship for the efficacy of many NSAIDs, including dexketoprofen (6–9). This raises an interesting and clinically relevant question: Could it be that when it comes to using NSAIDs in combination with triptans, more is not always better?

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Perhaps there is a ceiling effect, so that dose increases do not improve outcomes once an effective threshold dose has been reached.

Is this finding generalizable beyond the specific triptan and NSAID studied in this trial? It seems possible that the answer is yes. A similar result was observed in a trial that tested a fixed-dose combination of sumatriptan and naproxen. Adolescents with migraine were randomized to treat a moderate to severe attack with one of four possible treatments: placebo; a combination of 10 mg sumatriptan and 60 mg naproxen sodium; a combination of 30 mg sumatriptan and 180 mg naproxen; or a combination of 85 mg sumatriptan with 500 mg naproxen. The three active treatments were statistically significantly superior to placebo, but there was no clear evidence of meaningful differences among them (10).

Thus, two studies now provide reason to suspect that there might not be a dose-response relationship for efficacy outcomes when NSAIDs are used in combination with triptans. These are informative results because it is important to minimize the risks from a treatment that will be used repeatedly for exacerbations of a long-duration chronic condition. NSAIDs are not the benign drugs they were once thought to be. In addition to gastrointestinal side effects, many also appear to elevate the risk of cardiovascular events. In contrast to the lack of a dose-response relationship with efficacy outcomes, these adverse events seem to be more clearly dose-related (11).

How should clinicians use this information? Since it is important to treat headaches fully and adequately, this study should reinforce clinicians’ confidence in the value of combining triptans and NSAIDs for patients who do not achieve desirable results with either alone. It seems clear that adding an NSAID to a triptan does increase the proportion of migraine patients with desirable treatment outcomes, but a higher NSAID dose is not necessarily better than a lower dose. Instead, the principle that “less is more” seems likely to apply when adding NSAIDs to triptans. Future studies of these combinations should seek to refute or confirm the existence of this ceiling effect.

References