Headache pathophysiology: basic science

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COMBINATION THERAPY IN A MOUSE MODEL OF MEDICATION OVERUSE HEADACHE.

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Introduction: Triptans and non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as migraine therapies. Not all patients respond to triptan monotherapy, and it has been shown that using both triptans and NSAIDs together increase response rates. However, these drugs may be a risk factor for medication overuse headache (MOH) in migraine patients.

Objectives: Therefore, this study aimed to investigate the impact of combination therapy (sumatriptan and ibuprofen) in a preclinical mouse model of MOH.

Methods: Male C57BL/6J mice (N=38) were injected intraperitoneally with ibuprofen (80 mg/kg), sumatriptan (0.6 mg/kg), sumatriptan and ibuprofen in combination or vehicle control daily for 15 days. Hind paw mechanical withdrawal thresholds were measured every second day using von Frey filaments. On the testing day, mice received one of the four drugs intraperitoneally prior to habituation to the testing apparatus for 30 minutes. The left hind paw was tested in a blinded manner by application of filaments perpendicularly to the plantar surface, starting with a force of 0.4g using the up and down method until a positive response was noted. The mechanical threshold was calculated using the Claplan analysis method and analysed over time via an ANOVA. All animal testing occurred in low-light conditions, between 09:00 and 15:00 to avoid circadian variations.

Table:

Results: Repeated exposure to either sumatriptan (maximally at day 15 by 97.8 ± 0.83%; $F_{(1, 17)} = 272.9$, $P \leq 0.0001$) or ibuprofen (maximally at day 7 by 48.3 ± 7.85%; $F_{(1, 17)} = 13.08$, P=0.0021) decreased mechanical thresholds. The combination of sumatriptan and ibuprofen reduced mechanical thresholds (maximally at day 15 by 54.7 ±10.43; $F_{(1, 18)} = 7.304$ P=0.0146); however, the thresholds were significantly greater than the sumatriptan alone group ($F_{(1, 17)} = 31.44$, $P \leq 0.0001$).

Conclusion: Repeated exposure to either sumatriptan or ibuprofen daily for 15 days can induce mechanical hypersensitivity in mice indicative of a MOH-like phenotype. However, ibuprofen has an acute effect to reduce the mechanical thresholds of sumatriptan when tested 30 mins post ibuprofen. The combination of sumatriptan and ibuprofen had comparable effects to ibuprofen alone that resulted in modestly reduced mechanical thresholds compared to sumatriptan alone. It remains to be confirmed if repetitive ibuprofen impacts basal hyperalgesia independent of its acute analgesic activity.

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