Effect of Infusion of Calcitonin Gene-Related Peptide on Cluster Headache Attacks

SCIENCE

Clinical Research

Key Take-Away:

The study concluded that the calcitonin gene-related peptide provoke cluster headache attacks in active-phase episodic cluster headache and chronic cluster headache but not in remission-phase episodic cluster headache. These results suggest anti-CGRP drugs may be useful in cluster headache management.

Cluster headache is a chronic headache disorder with a prevalence of 0.5 to 1.0 out of the population of 1000. Cluster headache attacks are characterised by prominent ipsilateral cephalic autonomic symptoms (CAS), such as tearing, conjunctival redness, rhinorrhea or nasal congestion, ptosis, as well as the sense of agitation or restlessness. Most of the patients experiencing episodic cluster headache with month-long attack periods separated by remission periods. The remaining 10% to 15% of patients experience chronic cluster headache. Extended cluster headache periods dramatically hinders individuals with increased health care expenses. The initiating pathways for the cluster periods and individual attacks are still unknown. There is no doubt that treatment options are limited, and no disease-specific preventive medication exists.

The number of studies suggested the role of CGRP in the inducing the migraine. Furthermore, the literature indicated that CGRP antagonism with receptor antagonists or monoclonal antibodies stops and prevents migraine. Although phenotypically different, migraine and cluster headache showed the elevated plasma level of CGRP. The results of the previous studies confirmed the role of CGRP in the induction cluster headache attack and provided a novel target for the researchers to overcome the lack of drugs.

The findings from previous studies indicate that intravenous infusion of CGRP would stimulate the cluster headache attacks in patients with chronic cluster headache. To confirm these findings, Anne Luise H. et al. conducted a randomised, double-blind, placebo-controlled, 2-way crossover study.

Rationale behind research

- The number of previous studies reported the role of CGRP in the pathogenesis of cluster headache, but none of them evaluated the effect of CGRP on the induction of cluster headache.
- Therefore, in the current study, the authors used a CGRP infusion to test its role in the provoking the cluster headache.

Objective

The study was aimed to determine whether CGRP induces cluster headache attacks in episodic cluster headache in active phase, episodic cluster headache in the remission phase, and chronic cluster headache.

Methods

Study outcomes:

- **Headache Intensity and Questionnaire:** If any type of headache occurred, headache intensity was recorded. This was done at baseline (10 minutes before infusion start and at the time of infusion start) and after the intervention every 10 minutes until 1.5 hours (90 minutes after infusion start) on an 11-point numerical scale from 0 to 10.
- **Cluster Headache–like Attack Criteria:** Based on previous cluster headache provocation studies, the attacks were defined as provocation-related when occurring 0 to 90 minutes after infusion start. On study day 1 before infusion, the participants were asked to estimate their attack frequency the preceding 30 days retrospectively for measured vital signs, non-headache, and CAS.
- **Time period:** NA

Results

Outcomes

- **Patients With Active-Phase Episodic Cluster Headache:** During the 90-minute in-hospital phase, 8 and 1out of 9 patients with active-phase episodic cluster headache reported a cluster like attack after CGRP (mean, 89%; 95% CI, 63%-100%) and placebo (mean, 11%; 95% CI, 0%-37%) respectively (P = .05). All except 1 attack occurred on the patient's usual side, and no bilateral attacks occurred. During CGRP induced attacks, all 8 patients experienced CAS and/or agitation. The mean AUC from 0 to 90 minutes for CGRP was 1.903 (95% CI, 0.842-2.965), and the mean AUC from 0 to 90 minutes for placebo was 0.343 (95% CI, 0-0.867) (P = 0.04).
- **Patients With Remission-Phase Episodic Cluster Headache:** During the 90-minute in-hospital phase, no patients with remission-phase episodic cluster headache reported cluster like attack after CGRP or placebo and also for the following 24 hours. For CGRP, the mean AUC from 0 to 90 minutes was 0.187 (95% CI, 0-0.571), and for placebo the mean AUC from 0 to 90 minutes was 0.019 (95% CI, 0-0.062) (P > .99).
- **Patients With Chronic Cluster Headache:** During the 90-minute in-hospital phase, after the CGRP 7 out of 14 patients with chronic cluster headache reported a cluster like attack (mean, 50%; 95% CI, 20%-80%) compared with none after placebo (mean, 0; 95% CI, 0%) (P = .02). All attacks occurred on the patient’s usual attack side, and no patients reported bilateral attacks. During CGRP induced attacks, 6 of 7 patients with chronic cluster headache experienced CAS.
- In the 30 days before study day 1, the 7 patients who did report a cluster like attack after CGRP reported a median attack frequency of 33. The 7 patients who did not report attack after CGRP had a median attack frequency of 7.5 (Figure 2). The mean AUC from 0 to 90 minutes for CGRP was 1.214 (95% CI, 0.395-2.033), and the mean AUC from 0 to 90 minutes for placebo was 0.036 (95% CI, 0-0.114) (*P* = .01).

Discussion

The results of the current study suggested that CGRP provoked cluster headache attacks only in the active phase and not in patients in remission. Overall, the findings propose that (1) CGRP plays a crucial role in the initiation of a single cluster headache attack and (2) suggested a possible clinical efficacy of anti-CGRP (e.g., specific monoclonal antibodies).

The previous studies reported elevated ictal plasma levels of CGRP in patients with cluster headache. This elevated CGRP reached to normal after oxygen inhalation and subcutaneous sumatriptan injection. CGRP is known as one of the most potent vasodilators, and it innervates human cranial arteries. Cyclic adenosine mono-phosphate mediates the intracellular signalling cascade after CGRP receptor activation. CGRP also regulates the activity of nociceptive trigeminal neurons as well as central structures that process trigeminal pain. Neurons in the trigeminal and sphenopalatine ganglia express CGRP, and CGRP is released on the thermocoagulation of the trigeminal ganglion. This recommends that CGRP is optimally located to play a role at both the nociceptive and parasympathetic end of the trigeminal-autonomic reflex. CGRP could exert its cluster headache–inducing abilities in 3 distinguishing ways. First, this may occur via vascular effects of CGRP, likely involving neurogenic inflammation. Second, CGRP receptor components are also found in the human trigeminal ganglion, which has been suggested as the possible target for the CGRP receptor antagonists. Third, neurons in the sphenopalatine ganglion express CGRP and its receptor components. The efferent outflow of CGRP from sphenopalatine ganglia reported as the initiating mechanism of cluster headache attacks. Interestingly, in the present study, the median time to onset of parasympathetic symptoms preceded the median onset of head pain. These data indicate that CGRP may induce parasympathetic outflow and trigger cluster headache attacks.

Previous studies revealed that glyceryl trinitrate induced cluster headache during the active phase. Glyceryl trinitrate produced attacks in 20 to 78% of patients of chronic cluster headache. The results of the current study extend these findings showing that CGRP did not provoke cluster headache attacks during remission. These data suggest peripheral mechanisms alone cannot explain CGRP-induced attacks and central mechanisms altering the provocability threshold by CGRP should be considered. The remarkable circadian/circannual periodicity in cluster headache, as well as neuroendocrine changes, hint to the hypothalamus as responsible for altering the provocability threshold. Brain imaging studies have generated strong support for this hypothesis. Activation of the posterior hypothalamus was seen during cluster headache attacks.

Additionally, structural deformities in the same region were detected using voxel-based morphometry magnetic resonance imaging in patients with cluster headache. However, later more extensive studies were unable to reproduce this. These controversies were notwithstanding, deep brain stimulation studies showed that continuous posterior hypothalamus stimulation aborts clusters. This suggests that direct neuronal inhibition in the hypothalamus is not responsible for the success of deep brain stimulation. Preferably, the hypothalamus may modulate the system lowering the provocability threshold down to allowing a peripheral trigger to set off attacks.

Conclusion

In conclusion, it was demonstrated that CGRP provokes cluster headache attacks during the active phase in patients with cluster headache. The results also guardedly suggest the efficacy of CGRP antagonism in the treatment of cluster headache.

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Therapeutic, Calcitonin Gene-Related Peptide, Cluster headache, Headache Intensity and Questionnaire, Cluster Headache–like Attack Criteria