Supplementary Online Content

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eAppendix. Supplementary methods and results

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplementary methods and results

Methods

Balanced allocation, blinding and randomization

Allocation was done on study day one and participants received the opposite on day two. Allocation was balanced to ensure approximately even numbers of participants receiving CGRP first and placebo last or vice versa. The regional central pharmacy prepared and randomized the experimental drug in a balanced fashion. CGRP and placebo vials were completely identical and all participants and study investigators were blinded to the content of the vials. The randomization code remained in the hospital during the study and was unavailable to investigators until study completion.

Cluster headache-like attack criteria

Experimentally provoked cluster headache by pharmacological substances is not spontaneous and therefore cannot fulfil strict IHS cluster headache attack criteria. The following facts are important in defining criteria for induced cluster-like attacks. First, the cluster-like attacks reported are triggered by a pharmacological substance and can therefore not be spontaneous even if phenotypically similar to spontaneous attacks. Secondly, for ethical reasons we cannot deny patients attack treatment while awaiting pain intensity to become severe

Cephalic autonomic symptoms and non-headache symptoms

We recorded the following cephalic autonomic symptoms typical for cluster headache; conjunctival injection, lacrimation, rhinorrhea, nasal congestion, eyelid edema, facial sweating, ptosis and miosis. In addition, we recorded a feeling of inner restlessness.

Vital signs

We measured mean arterial blood pressure (MAP) and heart rate using an auto-inflatable cuff (Microlife, Widnau, Switzerland) every 10 min from T-10 until T90 and monitored ECG (Cardiofax V Nihon Kohden, Tokyo, Japan) continuously during the same time interval.

Statistical analysis

We performed the following calculation (alpha multiplier 1.96, beta multiplier 0.842):

n = (((a+b)2(p1q1+p2q2)/x2

n = (1,96+0,842) 2 x (0,20x0,80 + 0,34x0,66) / 0,462

n = 14,26

Results

Because five subjects were excluded form final analyses the balanced allocation resulted in the following: 18 participants received CGRP on study day one and 14 received placebo on study day one. We found no carry over effect randomization to CGRP on study day one vs placebo on study day 1 on ($p = 1.000$ for episodic active phase and remission phase cluster headache patients, $p = 0.103$ for chronic cluster headache patients).

Preventive treatment

Five out of seven chronic cluster headache patients who reported attacks took preventive medication and four out of seven patients who did not report attacks took preventive medication.

Four out of nine active phase episodic cluster headache patients reported using preventive treatment at stable doses for at least one week before entering the study. Five active phase episodic cluster headache patients were not on any preventive treatment preceding or during the study.

Two of nine remission phase episodic cluster headache patients reported using preventive treatment at stable doses for at least one week before entering the study.

Patients with remission phase episodic cluster headache

Two patients (one male, one female) were excluded from final analysis due to coexisting migraine with and without aura. None of the patients developed cluster headache attacks on CGRP or placebo day. Furthermore, none of the patients reported any migraine-like attacks on CGRP or placebo day.

Patients in active disease phase

As an exploratory analysis we pooled together patients in active disease phase; episodic cluster headache active phase and chronic cluster headache patients. Fifteen of 23 active phase patients developed a cluster-like attack after CGRP (mean 65%, 95% CI 44-86%) compared to one after placebo (mean 4%, 95% CI 0-13%) (P=0.001). Only one patient reported a cluster headache attack on placebo day. Thus, we did not conduct statistical tests on difference in time to peak headache intensity between experimental days.

Vital signs

CGRP increased heart rate compared to placebo in active phase episodic cluster headache (P=0.020), chronic cluster headache (P=0.002), and remission phase episodic cluster headache (P=0.003) patients. No difference in MAP was found between CGRP and placebo in active phase episodic cluster headache, chronic cluster headache, and remission phase episodic cluster headache patients (P>0.05).