CGRP: Clinical Commentary

Sandor, P S
Sandor PS.
Triptans have brought a considerable advancement into migraine therapy and did indeed change the lives of numerous sufferers. They are, in general, safe and well tolerated. However, vascular patients cannot take advantage of treating their migraines with triptans, due to some degree of vasoconstriction that is associated with their use. There are some postmarketing reports of serious vascular events in patients, mostly with multiple vascular risk factors (for review Dahlöf 2002). Other side effects, such as dizziness, nausea, fatigue, chest symptoms, and paresthesias, prevent some patients from using triptans. CGRP antagonists, a new class of substances, might have the potential to have a better safety and tolerability profile, but an efficacy comparable to triptans. The most relevant clinical publications in this context will be discussed below. The substances covered will be BIBN 4096 (olcegepant), an iv compound, and oral MK-0974.

**CALCITONINGENE–RELATEDPEPTIDE RECEPTORANTAGONISTBIBN4096BSFORTHE ACUTETREATMENTOFMIGRAINE**


Olesen J, Diener H-C, Hustede IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko LM, for the BIBN 4096BSClinicalProof ofConceptStudyGroup

Abstract: In this proof of concept study, a total of 126 migraine patients were treated with placebo (n =41), or with 0.25, 0.5, 1, 2.5, 5, or 10 mg of intravenous BIBN 4096 following a complex, group-sequential adaptive treatment assignment design that allowed to minimize the number of treated patients. It was an international multi-center double-blind randomized trial. Treatment response was defined as a reduction of moderate or severe headache to mild or none at 2 hours (=primary end point). The verum group as a whole had a treatment response of 60%, compared with 27% in the placebo group, which was statistically significant. Following the study design that included up-or down-dosing in a subsequent treatment group depending on the response to the previous dose resulted in the selection of the 2.5-mg dosage, which showed a response of 66%, meaning that this is the lowest dosage superior to placebo. The only side effect that occurred in more than 2 patients in this study was mild paresthesia (in 8 patients), which suggests excellent tolerability of the substance. In this study, there was no safety problem monitored.

Comment: This can be considered as a milestone study, as it shows efficacy of a CGRP antagonist, a drug which belongs to a new class of substances, in the acute treatment of migraine. Importantly, the tolerability seems to be excellent. As a proof of concept study following a creative design with the aim to minimize the number of participants, and therefore a small number of treated patients, it is difficult to compare the magnitude of clinical response to previous studies with triptans. Nevertheless, this study is very promising as it suggests that CGRP antagonists are a class of substances that for the acute treatment of migraine might compete with the triptans, and possibly win.
THE CGRP-ANTAGONIST, BIBN4096B DOES NOT AFFECT CEREBRAL OR SYSTEMIC HEMODYNAMICS IN HEALTHY VOLUNTEERS


Petersen KA, Birk S, Lassen LH, Kruse C, Jonassen O, Lesko L, Olsen J

Abstract: This is an experimental study in 7 healthy volunteers, in a placebo controlled, double-blind, crossover design, with the participants receiving placebo, 2.5 mg or 10 mg of BIBN4096 intravenously on 3 different days. The assessment of cerebral and systemic hemodynamics was done using transcranial Doppler measuring blood flow velocity of the middle cerebral artery, 133-Xenon inhalation SPECT to measure global and regional cerebral blood flow, high-resolution ultrasound to measure the diameter of the temporal and the radial artery. None of these methods resulted in any difference between the three treatment groups, suggesting that BIBN4096 has no vasoactive effect.

Comment: These results are important because, as discussed above, triptans are contraindicated in the group of patients with a significant vascular risk, exactly because of their vasoconstrictive properties. It might be remarked that a study with such a small number of participants has to have a low power, and as the authors present a negative result, the power and type 2 error become important in the interpretation of the results. These are convincing, nevertheless, as the authors (1) have presented the data showing the superimposed results in the 3 treatment groups and (2) have undertaken additional calculations in which they compare placebo with the highest dose BIBN4096, indicating that the study was powered to detect a vasoconstriction of larger than 5.4% and a vasodilatation larger than 3.5%. Therefore, these results can be taken as valid evidence to support the notion that BIBN4096 is not vasoactive in the studied population.

BIBN4096B ANTAGONIZES HUMAN a-CALCITONIN-RELATED PEPTIDE–INDUCED HEADACHE AND EXTRACEREBRAL ARTERY DILATATION


Petersen KA, Lassen LH, Birk S, Lesko L, Olsen J

Abstract: This is another human experimental study of the same group as the previously discussed one. In a double-blind, crossover, placebo-controlled design, headache and vasodilation are elicited using human a-calcitonin gene-related peptide (1.5 mg/minute over 20 minutes) in 10 healthy volunteers, and are pretreated with BIBN4096 i.v., or placebo. As in the previously discussed study, cerebral and systemic hemodynamics were assessed using transcranial Doppler measuring blood flow velocity of the middle cerebral artery, global and regional cerebral blood flow were measured using 133-Xenon inhalation SPECT, and the diameter of the temporal and the radial artery was measured using high-resolution ultrasound. Systemic hemodynamics (blood pressure) as well as end tidal CO2 pressure and headache were monitored. Six out of 10 participants reported headache after placebo pretreatment, but none after BIBN4096 pretreatment. Intracranially, CGRP infusion was followed by an increase of regional cerebral blood flow, as well as an increase in middle cerebral artery diameter, without any difference between BIBN4096 and placebo pretreatment. CGRP-induced extracranial vasodilation was inhibited by BIBN4096 pretreatment in both temporal and radial arteries.

Comment: This study, which is methodologically similar to the above-discussed one, addresses a somewhat different question of effects on CGRP-induced changes. The results of this study suggest that, in healthy volunteers, pretreatment with the studied CGRP antagonist is able to counteract CGRP-induced headache as well as extracranial vasodilation, while intracranial vasodilation is unchanged by the used CGRP antagonist. In line with the proof of concept study discussed above, in which BIBN4096 was found to be effective to treat migraine, in this study, the same substance was able to prevent CGRP-induced headaches also in healthy volunteers. As only extracranial, but not intracranial, CGRP-induced changes of blood flow were prevented by BIBN4096, the question can be asked whether the majority of the pathophysiological effect happens in other structures than intracranial arteries.

RANDOMIZED CONTROLLED TRIAL OF AN ORAL CGRP RECEPTOR ANTAGONIST, MK-0974, IN ACUTETREATMENT OF MIGRAINE
Abstract: In this multicenter, randomized, double-blind parallel group study with an adaptive dose-ranging design in 2 stages, patients were treated with the oral CGRP antagonist MK-0974 in the dosages 25, 50, 100, 200, 300, 400, or 600 mg, with rizatriptan 10 mg, or with placebo. A total number of 420 patients were enrolled in the study. The primary outcome measure was efficacy in terms of reduction of moderate to severe migraine to mild or no headache. The dosages of 200 mg or below of MK-0974 were eliminated in the adaptive dose-ranging procedure after 192 patients had been treated in the first step. For the remaining 3 dosages, there was a significantly better effect for the primary outcome parameter \( (P=0.015) \); for the different dosages (with patient numbers) pain relief was as follows: 300 mg \((n=38)\) 68.1\%, 400 mg \((n=45)\) 48.2\%, 600 mg \((n=40)\) 67.5\%, rizatriptan 10 mg \((n=34)\) 69.5\%, and placebo \((n=115)\) 46.3\%. Therefore, efficacy of MK-0974 was comparable to rizatriptan 10 mg; however, the study was not sufficiently powered to make a statistical statement on the efficacy of treatment groups. Interestingly, the numerical values for the very conservative efficacy measure “sustained pain free” (pain free between 2 and 24 hours) were higher in the MK-0974 groups than in the rizatriptan group. Adverse events in the MK-0974 300-600 mg groups were nausea, dizziness, and somnolence; all of them were mild and only nausea was more frequent compared with the placebo group.

Comment: This study of the oral MK-0974 is the logical next step to the proof of concept study with the intravenous CGRP antagonist BIBN4096. Promisingly, tolerability was excellent and efficacy appeared to be comparable to rizatriptan, which had been among the most efficacious triptans in the meta-analyses, although sufficiently powered comparative studies are yet to be done. While this commentary is written, several phase 3 studies of the same substance are on the way.

Peter S. Sandor, MD

Headache & Pain Unit, Neurology Department, University Hospital Zurich, Frauenklinikstrasse 26, 8091 Zürich, Switzerland

References