CNS Drug Reviews
Vol. 11, No. 1, pp. 69–76

Clinical Data on the CGRP Antagonist BIBN4096BS for Treatment of Migraine Attacks

Lars Edvinsson

Department of Internal Medicine, Lund University, Lund, Sweden

Keywords: BIBN4096BS — CGRP antagonists — Migraine.

ABSTRACT

Basal studies have shown that calcitonin gene-related peptide (CGRP) is a major sensory neuronal messenger in the trigeminovascular system, the pathway conveying intracranial pain. In migraine and cluster headache attacks, CGRP is released in parallel with the pain and successful treatment of the attacks abort both the associated pain and the CGRP release. The search for a potent small molecule CGRP antagonist has been successful and such an agent has been tested in preclinical and clinical studies. The aim of the present study was to examine current knowledge on the clinical pharmacology of systemic BIBN4096BS, which has been shown in man to abort acute migraine attacks as well or better than oral sumatriptan. BIBN4096BS is a specific and potent CGRP receptor antagonist in humans. In safety and tolerability studies the substance is well tolerated with no or only mild side effects. In acute migraine attacks the overall response was 66% with the drug and 27% with placebo. A difference as compared to placebo was seen at 30 min; the response was still rising at 4 h suggesting a long duration of action. At 24 h the pain-free rate was better than that with triptans, suggesting a lower grade of rebound and perhaps even a prophylactic possibility.

INTRODUCTION

Migraine is a common episodic neurological disorder, which is well characterized clinically; it affects 12–17% of the Western population. The disorder is characterized by headaches that can be severe, throbbing and unilateral, frequently accompanied by symptoms including photophobia, phonophobia, nausea and vomiting (30). In some attacks, headache is preceded by an aura, which involves neurological symptoms of which the most common are visual, sensory and speech disturbances.

Address correspondence and reprint requests to: L. Edvinsson, M.D., Ph.D, Department of Internal Medicine, University Hospital, S-221 85 Lund, Sweden.
Tel.: +46 (46) 17-14-84; Fax: +46 (46) 18-47-92; E-mail: lars.edvinsson@med.lu.se

Current theories propose that migraine-specific triggers promote a primary brain dysfunction, which evokes changes in the vicinity of intracranial vessels and results in the activation of perivascular trigeminal nerves (7). These nerves provide sensory information from the major blood vessels to the central nervous system (CNS). Any hypothesis regarding pain in primary headache disorders rests on the classic observations by Ray and Wolff which describe painful sensations as a result of mechanical, thermal or electrical stimulation of large cerebral arteries, venous sinuses, and dural arteries (26). These pain-sensitive supratentorial structures are supplied by bipolar nerve fibers that arise in the trigeminal ganglion. The fibers and the cell bodies contain a number of messengers but calcitonin gene-related peptide (CGRP) is the one most frequently expressed (12). A role of the trigeminovascular system in the transmission of nociceptive information to the CNS is thus a viable proposition. Antidromic or local mechanical stimulation of sensory nerve endings results in vasodilatation via the release of vasoactive materials such as CGRP (5,7).

In migraine and cluster headache, there is a clear association between the headache and the release of CGRP, but not with any of the other neuronal messengers that are stored to a lower degree in this system. The background and current status regarding the role of CGRP in the cranial circulation has recently been reviewed (5). Several primary headaches, such as migraine, cluster headache and chronic paroxysmal hemicrania are associated with increased levels of CGRP in the cranial venous outflow during the pain (1,10). Furthermore, CGRP in the antecubital vein increases by 25–30% during nitroglycerin-induced migraine attacks and the increase in CGRP correlates with the headache intensity (17). Furthermore, it has been shown that administration of sumatriptan or rizatriptan decreases the plasma CGRP concentration both in spontaneous attacks and in migraine attacks elicited by nitroglycerin administration (5,16). This decrease is present only in those patients whose headache showed parallel clinical improvement (11,16). In patients whose headache did not improve, the CGRP concentrations failed to show a decrease after the administration of nasal sumatriptan (11,16). Furthermore, plasma CGRP significantly correlates with headache scores also after sumatriptan treatment. These results support a close relationship of CGRP release and migraine headache (18).

With data like these Boehringer Ingelheim scientists were stimulated to produce a potent and specific CGRP receptor antagonist BIBN4096BS (piperidinecarboxamide, N-[2[[5-amino-1-[[4-(4-pyridinyl)-1-piperazinyl]carbonyl]pentyl]amino-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-4-(1,4-dihydro-2-oxo-3(2H)-quinazolinyl) (4). This work resulted in studies of its clinical pharmacology and toxicology demonstrating efficiency and a low degree of cardiovascular side-effects. Further support for the central role of CGRP in migraine pathophysiology was recently presented; BIBN4096BS intravenously was found to be as efficacious as oral sumatriptan in the relief of acute attacks of migraine (21). This review article compiles available information on BIBN4096BS in humans.

PHARMACOLOGY

Both peptide ($CGRP_{8–37}$) and non-peptide ("compound 1" and SB-273779) compounds effectively antagonize CGRP responses *in vivo* and *in vitro* (5). These antagonists are, however, not suitable for human use. The dipeptide BIBN4096BS (Fig. 1), however, is

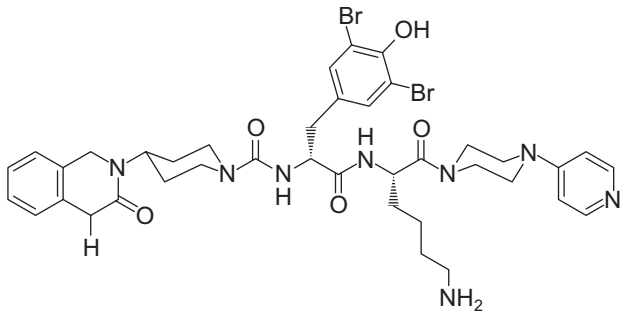

Fig. 1. Chemical structure of BIBN4096BS. Reproduced from ref. 4.

now a well-characterized antagonist, which is highly selective and potent in both animal and human experiments (4–6,32). Below are described some of the preclinical data leading to this. Although the trigeminal ganglion contains many signal molecules, it is CGRP that is most abundant in man (12) and notably the intracranial arteries respond more potently to CGRP with dilatation than peripheral and extracranial vessels do (5).

CGRP relaxes both peripheral and middle meningeal arteries *in vivo*, and lowers blood pressure (25). Local stimulation of the perivascular nerves around the middle meningeal artery relax upon electrical stimulation and this effect can be blocked by local or systemic administration of CGRP antagonists such as BIBN4096BS (25) or by triptans (31). Interestingly, the nearby located cerebral arteries also relax, but to a lower degree. BIBN4096BS did not block this relaxant effect (25). Analysis of the local cerebral blood flow showed small and uncertain effects of CGRP per se suggesting poor penetration across the blood-brain barrier (1,25,29).

MECHANISM AND SITE OF ACTION OF BIBN4096BS

BIBN4096BS is a large hydrophilic molecule and is, therefore, not likely to pass the blood-brain barrier easily; predicatively it might at best pass very slowly and in small amounts. There are no studies available which provide a direct measure of the passage of BIBN4096BS across the blood-brain barrier. In contrast to the cerebral vessels, the meningeal vessels have no known barrier and BIBN4096BS is, therefore, likely to diffuse freely into the wall of these vessels (8) as has been seen *in vivo* (25).

Using SK-N-MC membranes expressing the elements of the CGRP receptors, calcitonin receptor-like receptor (CRLR) and receptor activity modifying protein (RAMP1), BIBN4096BS was found to have high affinity for the $CGRP_1$ receptor (4,6,32). The compound has a 10-fold higher affinity for the $CGRP_1$ receptor as compared to the $CGRP_2$ receptor (32). Since receptors with a $CGRP_1$ profile are situated primarily on the smooth muscle cells of cerebral arteries (22), systemically administered BIBN4096BS has to pass the BBB to inhibit vasodilatation of cerebral arteries and arterioles. It has been shown that dural arteries respond to systemically given CGRP and BIBN4096BS can completely block this as well as the vasodilator response to local electrical stimulation (25). Electrical stimulation primarily releases CGRP but also other neuronal messenger peptides such as

substance P and pituitary adenylate cyclase-activating peptide (PACAP) (3,7,12), the latter messengers may account for the remaining 20% of the dilatation that is not inhibited by BIBN4096BS. Cerebral (pial) vessels investigated can be defined as second order arterioles since they do not exceed the size of 100 μm (13). Systemic CGRP or local electrical stimulation induces dilatation of cerebral arteries, which was not significantly abolished by pretreatment with BIBN4096BS (25). However, the response was reduced and a *post hoc* analysis showed a significant difference between the control response and the CGRP-elicited responses after the highest doses of the antagonist. The CGRP antagonist did not significantly inhibit the increase in local cerebral blood flow seen after intravenous infusion of CGRP. A minor reductive tendency of αCGRP was, however, observed (25). These data on BIBN4096BS suggest that the blocker does not freely pass the blood-brain barrier in the rat, but is very effective in preventing vasodilatation of vessels without this feature.

SAFETY, TOLERABILITY, AND PHARMACOKINETICS

A study of BIBN4096BS following single intravenous administration in rising doses (0.1 to 10 mg) in 55 healthy volunteers (age: 21 to 47 years, either sex) has been published (15). It was carried out in one center in a double-blind, randomized and placebo-controlled manner. There was no significant effect on supine blood pressure and only at the highest dose (10 mg) did BIBN4096BS produce a significant increase in the standing blood pressure. This is of principal interest since CGRP has been discussed in relation to hypertension (19). CGRP has been thought to be part of a counterbalance mechanism operating at high blood pressure and thus could act as a protective mechanism in high-pressure situations. BIBN4096BS did not induce changes that were considered clinically of significance for the blood pressure regulation. In addition, the respiratory rate and routine clinical chemistry data were without significant alterations.

During infusion of BIBN4096BS there was a statistically significant increase in supine pulse rate but it had no clear relation to the plasma levels of the drug (15). In addition, there was no change in EKG or in heart rhythm related to the circulating BIBN4096BS. Only a minor increase in heart rate was seen at 8 hours, but at this time point the drug was no longer detectable in the plasma. Detailed analysis using 12-lead EKG and detailed QTc study confirmed these findings. In addition, the forearm blood flow was studied with venous occlusion plethysmography (15). Some fluctuations in blood flow were seen but they were regarded as related to the uncertainty of the method, rather than to the drug.

The safety and tolerability of BIBN4096BS have been included in other studies and essentially they are in concert with the above data (23,24). However, blockade of a strong endogenous vasodilator such as CGRP carries the inherent risk of causing unwanted side effects such as local vasoconstriction, if there is a tonic influence on any particular system. With this in mind Petersen and colleagues studied in healthy volunteers middle cerebral artery velocity with transcranial doppler, diameter changes in radial and superficial temporal arteries with high-resolution ultrasound, regional cerebral blood flow with SPECT, as well as blood pressure and heart rate (23,24). They did not observe any vasoconstrictor effect of BIBN4096BS in cerebral or systemic circulations during infusions of the drug at 2.5 or 10 mg over a 10-min period. Thus, in agreement with animal data CGRP does not appear to have a tonic influence on the circulation. This CGRP antagonist can, therefore,

be given for acute attacks with only minor risk of unwanted vascular reactions (23). In healthy volunteers CGRP induces typical symptoms often seen with vasodilators: flushing, heat sensations, palpitations, conjunctiva injection (red eye) and headache (24). These effects have been seen in previous studies following infusion of CGRP (14,28). All these effects were abolished by a prior administration of 2.5 mg of BIBN4096BS (23,24). Furthermore, global or regional cerebral blood flow increased significantly after CGRP administration; this effect was however, not blocked by BIBN4096BS (24). This suggests that the antagonist does not pass the blood-brain barrier, and agrees well with the transcranial Doppler analysis, which revealed a CGRP-induced 9.3% increase in the resting diameter of cerebral arteries. When BIBN4096BS was given before the CGRP administration, an increase in diameter was still seen, but it was not significant possibly due to a low number of patients. On the other hand, the CGRP effects were marked in the extracerebral vessels and the effect of infused CGRP was blocked by BIBN4096BS (24); these findings were in agreement with a detailed study in rats (25).

ADVERSE EVENTS

There were 16 adverse events (AEs) reported by 8 of 41 active-treated volunteers after a single dose administration of BIBN4096BS as compared to 5 AEs in 4 of 14 placebo-treated subjects (15). Higher AE incidence rates were reported for 5 and 10 mg of BIBN4096BS; two-thirds of the AEs were reported at the highest dose, 10 mg of BIBN4096BS. Flushing, a feeling of warmth, numb feeling in hands, and congestion in the head were reported by three female volunteers. Paresthesia was the single most frequent AE. The AEs were generally considered mild and only in two cases were two AEs considered moderate; these AEs were transient flushing during and after infusion of the drug as well as lower abdominal pain. The latter occurred at more than 35 h after administration of the CGRP receptor antagonist.

In the double-blind randomized trial of 126 migraine patients BIBN4096BS caused AEs in 20% of the subjects on active drug and in 12% of subjects on placebo (21). The most frequent side effects were paresthesia (8%), nausea (2%), headache (2%), dry mouth (2%), and abnormal vision (2%). These effects were all regarded as mild and transient. There were no alterations in clinical chemical data.

PHARMACOKINETICS

The plasma concentration-time course of infused BIBN4096BS has been examined for the two highest doses (15); the drug behavior was considered to have multicompartmental disposition characteristics. The mean maximum concentration (C_{max}) values were dose-proportional. BIBN4096BS exhibited a total plasma clearance of about 12 L/h, an apparent volume of distribution at steady state of 20 L, and a terminal half-life of 2.5 h. Interindividual variability was moderate with a coefficient of variation of 45% as based on the area under the plasma concentration-time curve (15). About 15% of the drug appeared in the urine; the mean renal clearance was 2 L/h, which suggests that renal excretion plays only a minor role in the elimination of BIBN4096BS.

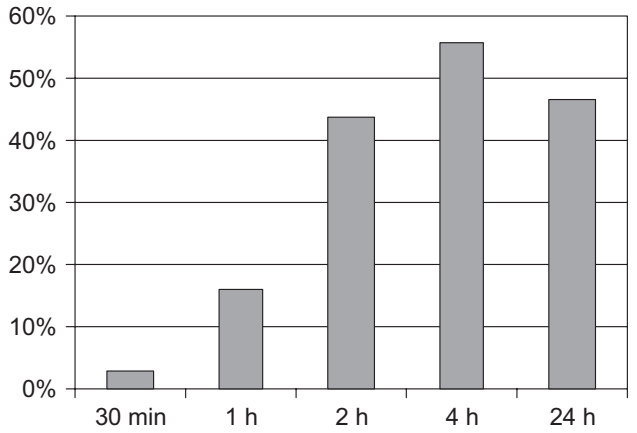

Fig. 2. Percentage of headache-free subjects at various time points. Updated from ref. 21.

EFFECTS ON ACUTE SPONTANEOUS MIGRAINE ATTACKS

Generally BIBN4096BS was found to be effective in the treatment of migraine attacks at up to 6 h after their onset (21). Thus, the primary end point of the study was the headache response at two hours after treatment. The response was defined as a reduction in headache from severe or moderate to mild or no headache at this time point. Secondary end points were the responses at other time points, the headache-free rates, and the rates of sustained response over a 24-h period, the relief of associated symptoms, and time to meaningful relief, degree of clinical disability, use of rescue medication, frequency of AEs and other clinical symptoms.

The authors used a group-sequential adaptive treatment-assignment design to minimize patients to non-efficacious doses. The goal of this approach is to identify the lowest dose of a drug that is superior to placebo and has been used previously in the study of potential treatments for acute migraine (27). This resulted in the selection of the intravenous 2.5 mg dose as the optimum dose. The overall rate of response was 66% and the rate of response to placebo was 27%. A difference between BIBN4096BS and placebo was obvious already at 30 min at doses of 2.5 to 10 mg. However, the response was still increasing at 1,2 and 4 h both with regard to response rate and headache-free rates (Fig. 2). The placebo effect was identical to that seen when comparing with published oral triptan studies (9). In addition, when comparing with the effect of sumatriptan tablets (50 or 100 mg) in a meta-analysis of triptans (9) a similar efficacy was noted. The speed of onset was fairly rapid since it was given as an infusion but the rate of response was increasing over the duration of study which seems to differ with that of subcutaneously administered sumatriptan, both in reaching the peak response and the maximal response, which were higher for sumatriptan.

Among the secondary endpoints the pain-free rate is today an important aspect in headache research (9). The response rate to BIBN4096BS was 44% at 2 h and 56% at 4 h; at the same time the placebo effect was 2% and 10% which leaves us with a good headache-free rate of 42 to 46% (in the meta-analysis it was about 20% for sumatriptan) (9). This

would indicate superiority of BIBN4096BS. In addition, the sustained 24 h headache–free rate was 47% (placebo 15%), which also compares well with the sumatriptan pain-free rate of 20% (9). Other secondary end-points (nausea, photophobia, photophobia, inter alia) all improved in parallel with the extent of the response to the treatment. The rate of recurrence was 19% as compared to placebo rate of 46%, and this is clearly lower than that of the triptans (usually around 28%) (9).

In viewing Table 2 from the Olesen paper (21) it seems there is a prolonged effect of the CGRP antagonist which may prove to be of value in the treatment of migraine, i.e., a long-lasting response. This may be an observation that differentiates the CGRP antagonist from triptans and may suggest not only less rebound headache but perhaps also a prophylactic possibility (Fig. 2).

CONCLUSIONS

A large body of evidence exists to show that CGRP has a pivotal role in migraine pathophysiology (5,7). The encouraging results obtained in the "proof of concept" study show that the CGRP antagonistic approach holds promise. However, BIBN4096BS, the most potent and selective of the published CGRP antagonists, displays limitations in site of action and possible diversity in potency towards the different subtypes of CGRP. In a rat model of vascular headache (25) and in a study of healthy volunteers (23), BIBN4096BS does not appear to pass the blood-brain barrier freely and may, therefore, exert its antagonistic actions on extracerebral arteries and neuronal structures (parts of the trigeminovascular system outside the CNS). Although it may be tempting to propose a hypothesis on the site of origin of migraine headache we still need more data to support it (7). The site of the antimigraine effect of BIBN4096BS, as judged from the available data, suggests that it does not have to reach the CNS to exert its therapeutic action and thereby its side effects may be limited. In addition, the main competitors in the field of migraine are the triptans and they have received much attention with regard to their cardiovascular safety (3,20). Future studies may show other mechanisms of action of BIBN4096BS, but at this stage this CGRP antagonist appears to act primarily as a blocker of neuronal transmission in the trigeminovascular system (2).

Acknowledgments. Supported by the Swedish Research Council (grant No. 5958).

REFERENCES

1. Baskaya MK, Suzuki Y, Anzai M, et al. Effects of adrenomedullin, calcitonin gene-related peptide, and amylin on cerebral circulation in dogs. *J Cereb Blood Flow Metab* 1995;15:827–834.
2. Brain SD. Calcitonin gene-related peptide (CGRP) antagonists: Blockers of neuronal transmission in migraine. *Br J Pharmacol* 2004;142:1053–1054.
3. Dodick DW. Introduction: Cardiovascular safety and triptans in the acute treatment of migraine. *Headache* 2004;44(Suppl 1):S1–S4.
4. Doods H, Hallenmayer G, Wu D, et al. Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist. *Br J Pharmacol* 2000;129:420–423.
5. Edvinsson L. Blockade of CGRP receptors in the intracranial vasculature: A new target in the treatment of headache. *Cephalalgia* 2004;24:611–622.

6. Edvinsson L, Alm R, Shaw D, et al. Effect of the CGRP receptor antagonist BIBN4096Bs in human cerebral, coronary and omental arteries and in SK-N-MC cells. *Eur J Pharmacol* 2002;434:49–53.
7. Edvinsson L, Uddman R. Neurobiology in primary headaches. *Brain Res Rev* 2005;48: In press.
8. Farachi FM, Kadel KA, Heistad DD. Vascular responses of dura mater. *Am J Physiol* 1989;257: H157–161.
9. Ferrari MD, Roon KI, Lipton RB, et al. Oral triptans (5-$HT_{1B/1D}$ agonist) in acute migraine treatment: A meta-analysis of 52 trials. *Lancet* 2001;358:1668–1675.
10. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine. Studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol* 1993;33:48–56.
11. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol* 1990;28:183–187.
12. Gulbenkian S, Uddman R, Edvinsson L. Neuronal messengers in the human cerebral circulation. *Peptides* 2001;22:995–1007.
13. Harper M, Bohlen HG, Rubin MJ. Arterial and microvascular contributions to cerebral cortical autoregulation in rats. *Am J Physiol* 1984;246:H17–24.
14. Howden CW, Logue C, Gavin K, et al. Haemodynamic effects of intravenous human calcitonin-gene related peptide in man. *Clin Sci* 1988;74:413–418.
15. Iovino M, Feifel U, Yong C-L, et al. Safety, tolerability and pharmacokinetics of BIBN4096BS, the first selective small molecule calcitonin gene-related peptide receptor antagonist, following single intravenous administration in healthy volunteers. *Cephalalgia* 2004;24:645–656.
16. Juhasz G, Zsombok T, Jakab B, et al. Parallel decrease in plasma calcitonin gene-related peptide (CGRP) concentration and migraine headache after sumatriptan treatment. *Cephalalgia* 2005;25:1–2.
17. Juhasz G, Zsombok T, Modos EA, et al. NO-induced migraine attack: Strong increase in plasma calcitonin gene-related peptide (CGRP) concentration and negative correlation with platelet serotonin release. *Pain* 2003;106:461–470.
18. Lassen LH, Haderslev PA, Jacobsen VB, et al. CGRP may play a causative role in migraine. *Cephalalgia* 2002;22:54–61.
19. Lind H, Edvinsson L. Enhanced vasodilator responses to calcitonin gene-related peptide (CGRP) in subcutaneous arteries in human hypertension. *J Human Hypertens* 2002;16:53–59.
20. MassenVanDenBrink A, Saxena P. Coronary vasoconstrictor potential of triptans: A review of *in vitro* pharmacologic data. *Headache* 2004;44(Suppl 1):S13–S19.
21. Olesen J, Diener HC, Husstedt IW, et al. Calcitonin gene-related peptide receptor antagonist BIBN4096BS for the acute treatment of migraine. *N Engl J Med* 2004;350:1073–1075.
22. Oliver KR, Wainwright A, Edvinsson L, et al. Immunohistochemical localization of calcitonin receptor-like receptor and receptor activity-modifying proteins in the human cerebral vasculature. *J Cereb Blood Flow Metab* 2002;22:620–629.
23. Petersen KA, Birk S, Lassen LH, et al. The novel CGRP-antagonist, BIBN4096BS does not affect the cerebral hemodynamics in healthy volunteers. *Cephalalgia* 2003;23:729.
24. Petersen KA, Lassen LH, Birk S, et al. The effect of the nonpeptide CGRP-antagonist, BIBN4096BS on human-alphaBGRP induced headache and hemodynamics in healthy volunteers. *Cephalalgia* 2003;23:725.
25. Petersen KA, Schindler M, Doods H, et al. Inhibiting effect of BIBN4096BS on cephalic vasodilatation induced by CGRP and electrical stimulation of dura mater in the rat. *Br J Pharmacol* 2004;143:697–704.
26. Ray BS, Wolff HG. Experimental studies on headaches, pain sensitive structures of the head and their significance in headache. *Arch Surg* 1940;41:813–56.
27. Roon KI, Olesen J, Diener HC, et al. No acute antimigraine efficacy of CP-122,288, a highly potent inhibitor of neurogenic inflammation: Results of two randomized, double-blind, placebo-controlled clinical trials. *Ann Neurol* 2000;47:238–41
28. Struthers AD, Brown MJ, Macdonald DW, et al. Human calcitonin gene related peptide: A potent endogenous vasodilator in man. *Clin Sci* 1986;70:386–393.
29. Suzuki Y, Satoh S, Ikegaki I, et al. Effects of neuropeptide Y and calcitonin gene-related peptide on local cerebral blood flow in rat striatum. *J Cereb Blood Flow Metab* 1989;9:268–270.
30. The International Classification of *Headache* Disorders. *Cephalalgia* 2004;24(Suppl 1):1–160.
31. Williamson DJ, Hargreaves RJ, Hill RG, et al. Sumatriptan inhibits neurogenic vasodilation of dural blood vessels in the anaesthetized rat — intravital microscope studies. *Cephalalgia* 1997;17:525–531.
32. Wu D, Eberlein W, Rudolf K, et al. Characterisation of calcitonin gene-related peptide receptors in rat atrium and vas deferens: Evidence for a [Cys(Et)(2,7)]hCGRP-preferring receptor *Eur J Pharmacol* 2000;400: 313–319.