University of Medicine and Pharmacy
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DOCTORAL THESIS

ABSTRACT

Research on therapeutic management of migraine

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2014

CONTENT

STATE OF KNOWLEDGE

Introduction

Migraine is characterized by a series of neurological conditions in which the brain and its associated tissues are involved as major players during an attack. This disorder, considered once exclusively a disorder of blood vessels, is seen nowadays, after compelling evidence provided by intense research, as a highly choreographed interaction between major inputs from both the peripheral and central nervous systems, with the trigeminovascular system and the cerebral cortex among the main players.

At present, the efforts are focused on the development of effective acute antimigraine medicines that act as inhibitors of the vasodilator mechanisms that could hopefully lead to fewer side effects and migraine preventive drugs that could prevent migraine auras.

Hystory of migraine

The history of migraine spans millennia, from the Neanderthal era to the Space Age[1].

With this long history, it is surprising that effective antimigraine drugs have been, until recently, limited in number. In the last decades, there have been big steps in the development of antimigraine drugs [2].

Classification, clinical features and diagnosic criteria of migraine

The basic research and clinical research has identified anatomical and functional systems involving the cephalic pain pathways, genetic abnormalities in some forms of primary headache (particularly migraine hemiplegic) and has prompted researchers and clinical specialists to revise the classification of headache disorder[3] finding thus new ideas for further research lines.

Migraine is a disorder of recurrent attacks that occur through a cascade of events subdivided in various stages (premonitory, aura, headache, and post-drome), over the course of several hours to days[4].

The diagnosis of migraine is a clinical task and is based upon a compatible history, physical examination, and fulfillment of the diagnostic criteria [3]. There are no diagnostic tests specific for migraine.

The clinical features that appear to be most predictive of migraine include nausea, photophobia, phonophobia, and exacerbation by physical activity. Some of migraine patients experience aura, a focal cerebral dysfunction consisting of visual, sensory, verbal or motor disturbance[5].

Pathophysiology of migraine

Three phases of migraine can be distinguished: the initiating trigger, the aura and the headache.
The neural and vascular mechanisms underlying the development of the initiating trigger phase are still unknown. Some studies indicate that the migraine trigger may be linked to inherited mutations in ion channels affecting membrane excitability and causing, thus, brain dysfunctions that are at the basis of a number of diseases termed channelopathies [6].

A neurovascular hypothesis can explains the subsequent events leading to the aura and headache symptoms [7]. Once the "migraine generator" has been switched on, regional cerebral blood flow decreases, possibly followed by a wave of cortical spreading depression[8]. This phenomenon is implicated in migraine aura.

The wave of cortical spreading depression seems also to initiate the activation of the nociceptive neurons (principally the first division of the trigeminal nerve) innervating cranial arteries in the dura mater of the skull with release of several vasodilator transmitters at this level and consequent cranial vasodilatation[9].
This activation is transmitted to the trigeminal nucleus of the brainstem and the upper divisions of the cervical spinal cord and it is relayed to central neurons that carry it to higher cortical centers, which register pain, photophobia and phonophobia. The activated trigeminal nucleus also connects with adjacent brainstem centres like the nucleus tractus solitarius, which upon activation, mediates nausea and vomiting[10].
Activation of trigeminal pain fibres also triggers the release of inflammatory mediators from their nerve endings reinforcing vasodilatation and perivascular nerve activity. The resulting neurogenic inflammation maintains the stimulation of the trigeminal nerve which causes the headache to persist [11].
Based on neurovascular hypothesis of migraine, acutely acting antimigraine drugs would constrict dilated cranial extracerebral blood vessels reduce neuropeptide release and plasma protein extravasation across dural vessels and inhibit impulse transmission centrally within the trigeminovascular system [12].

Treatment of migraine

The drugs used in the treatment of migraine can be divided into two groups: agents that abolish the acute migraine headache (acute antimigraine drugs) and agents aimed at its prevention (prophylactic drugs) [13]. Both groups include specific drugs and non-specific drugs.

The currently available acute antimigraine drugs are:

- non-specific drugs: non-steroidal anti-inflammatory drugs (NSAID's), opioids and antiemetics.
- specific drugs: the ergot-derivates and the triptans.

The new acute antimigraine drugs (Calcitonin gene-related peptide antagonists, 5-HT1F agonists, Glutamate receptor antagonists, VPAC/PAC receptor antagonists, Nitric oxide synthase inhibitors Gamma-aminobutyric acid agonists, Dopamine antagonists), in contrast to the currently available specific antimigraine drugs, do not induce vasoconstriction:

Migraine prevention is aimed at reducing the attack frequency, duration and severity. Secondary benefits include a better response to acute medication, a reduced disability and possibly a smaller risk of progressing to a more chronic or severe form of migraine [14].

The conventional and emerging prophylactic drugs are [15]:

- Antiepileptics
- Beta-blockers
- Antidepressants
- Antiserotoninergic agents
- Calcium antagonists
- ACE inhibitors and sartans
- Vitamins, minerals and herbal agents
- Botulinum toxin type A
- Tonabersat

PERSONAL CONTRIBUTIONS:

Personal research(i): the efficacy of telcagepant for acute treatment of migraine and its effect on migraine associated disability. A pilot study

Introduction

The current standard for acute migraine-specific treatments are the triptans which act on the serotoninergic system. Triptans are effective in the majority of patients with migraine [16] and generally well-tolerated.

Because of their potential vasocostrictive 5-HT1B-mediated effects, triptans are contraindicated in patients with coronary disease, cerebrovascolar disease, or significant risk factors for either [17].

Recent attention has focused on the possible role of calcitonin gene-related peptide (CGRP) in the pathophysiology of migraine[18]. CGRP receptor antagonists are not direct vasocostrictors [19] and may thereby confer an advantage over triptans in the acute treatment of migraine.

In clinical trials the CGRP receptor antagonists have demonstrated acute antimigrane efficacy comparable with existing triptan treatments and a godd tolerablity for treatment of a single attack [20, 21].

Correlation between migraine pathophysiology and study medication

Two main mediators (5-HT[22] and CGRP[23]) with their related receptors have been demostrated to be involved in migraine pathophysiology. This knowledge has led to the development of agents effective in the acute treatment of migraine [24].

The triptans that act at the serotonin receptors 5-HT1B, 5-HT1D, and, in part, at the 5-HT1F receptor are contraindicated in patients with cardiovascular disease or at risk for it.

Thus, it became evident that alternative pharmacological targets may be necessary in order to overcome the limitations of triptans.

Novel anti-migraine drugs, CGRP receptor antagonists (Gepants), seems to be effective in the acute treatment of migraine.[24].

Considerations on preclinical and clinical investigations of CGRP antagonists

Given the positive phase II trials on 2 different CGRP receptor antagonists[25, 26] the orally reported phase III data and their excellent tolerability[20], the possibility of a new class of specific anti-migraine medications become a reality.

CGRP receptor antagonists do not appear to exhibit vasoconstrictive properties and could be the first class of non-vasoconstrictor anti-migraine drugs.

The clinical trials have produced encouraging data in respect to the percentage of patients that were pain free after treatment and the 'low' recurrence rate.

Findings from recently completed clinical studies determined us to investigate the long term efficacy and tollerability of oral MK-0974 in the treatment of acute migraine and its effect on migraine related disability.

Personal research

We coducted a longitudinal observational study to examine the efficacy and tollerability of oral MK-0974 for the long term treatment of acute migraine and its effect on migraine related disability [27]**.**

The primary objectives were to estimate the efficacy of MK-0974 compared to rizatriptan as measured by painfreedom at 2 hours post-dose in the long term treatment of acute migraine.

The secondary objectives were to evaluate the safety and tolerability of MK-0974 compared to rizatriptan in the long term treatment of acute migraine.

Patients who met all the study entry criteria was enrolled and provided with study drug.

All patients were required to give written informed consent before undergoing any study procedures.

Patients were provided sufficient study medication to treat up to 8 migraine attacks per month for up to 12 months and were asked to record details of each attack in a patient diary.

The list of efficacy measurements were:

- Rating of headache severity, measured on the following verbal scale: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain.
- The presence or absence of associated symptoms (photophobia, phonophobia, nausea and vomiting).
- Functional ability, measured on the following scale: Ability to perform daily activities: Normal, Mildly impaired, Severely impaired, Unable to do Activities, requires bed rest.
- Headache return and the use of rescue medication

The list of safety measurements:

- Standard prestudy and poststudy screening (medical history and physical examination, vital signs, ECG, laboratory tests (including hematology, chemistry and urine analysis, and pregnancy test for females of child bearing potential)
- Subjective adverse experiences recorded in the patient diary.
-

Rationale for Dose Regimen

Based on findings from the Phase 2 study[25, 26] MK-0974 300 mg was chosen for this study.

Statistical Analysis

The primary efficacy endpoint was the pain freedom at 2 hours. The percentage of patient's attacks with pain freedom at 2 hours was summarized descriptively within each treatment group. Other efficacy endpoints, including pain relief at 2 hours, absence of associated symptoms at 2 and 24 hours (photophobia, phonophobia, nausea and vomiting) and 2- to 24-hour sustained pain freedom were summarized and analyzed with the same methodology. Subgroup analyses of the treatment differences in pain freedom and pain relief at 2 hours and 2- to 24-hour sustained pain freedom by patient's usual migraine treatment (triptan users and no triptan users) were also performed. Continuous data were shown as mean ± SD and categorical data as counts and percentages. Comparisons between preoperative and follow-up data were evaluated using ANOVA for repeated measures, while categorical variables were compared with the use of $\chi2$ test. Data were collected and reviewed in Microsoft Excel and statistical analysis was performed with SPSS 16.0 (SPSS Inc., Chicago, IL, USA). All 2-tailed $P < 0.05$ were considered statistically significant.

Results

Per-Patient analysis

Characteristics of the patients by treatment group are summarized in Table **Error! Reference source not found.**.

Tab. 5.3

	Telcagepant N=14	Rizatriptan N=10
Female gender	11 (78.6%)	7 (70%)
Age (years)	43.1 ± 7.3	42.3 ± 8.3
Migraine usually preceded by aura	4 (28.6%)	2 (20%)
Attacks/month in the last 2 months	3.6 ± 1.5	4.5 ± 2.4
Usual migraine treatment:		
Triptan	7 (50%)	4 (40%)
NSAID	2 (14.3%)	2 (20%)
NSAID and triptan	4 (28.6%)	3 (30%)
Other	1 (7.1%)	1 (10%)
None	0	0

The treatment groups had generally similar demographic profiles with a mean age of 42.7±8.8 years (range 27-61) and comprising predominantly women (78.6%).

Number of attacks treated during the study
Overall 384 attacks were treated with telcagepant and 320 attacks with rizatriptan. The mean number of attacks treated with study medication over the entire study was 26 vs 29, respectively.

Efficacy
Efficacy is summarized in Table **Error! Reference source not found.**.

Tab. 5.4

	Telcagepant N=384	Rizatriptan N=320	p-value
Pain freedom 2 hours	233 (60.7%)	222 (69.4%)	0.020
2 to 24-hour sustained pain freedom	364 (94.8%)	298 (93.1%)	0.441
Pain relief 2 hours	58 (15%)	157 (49%)	<0.001
No phonophobia 2 hours	23 (6.0%)	11 (3.4%)	0.163
No phonophobia 24 hours	2 (0.5%)	1 (0.3%)	0.874
No photophobia 2 hours	39 (10.2%)	10 (3.1%)	0.001
No photophobia 24 hours	4 (1.0%)	0	0.184
No nausea 2 hours	45 (11.7%)	15 (4.7%)	0.001
No nausea 24 hours	3 (0.8%)	0	0.316
No vomiting 2 hours	5 (1.3%)	2 (0.6%)	0.603
No vomiting 24 hours	0	0	-
Pain freedom 2 hours			
Triptan users	210 (54.7%)	208 (65%)	0.007
Non-triptan users	23 (6.0%)	14 (4.4%)	0.432

On all the 2-hour measures the results tended to favor rizatriptan. When looking at the later 24-hour measures (or 2- to 24-hour sustained pain freedom), the 2 treatments appeared more similar. Analysis of response by triptan-user subgroups, the differences were more clearly in favor of rizatriptan in triptan-users while among non-triptan-users, the 2 treatment groups were more similar.

The functional ability is summarized in Table **Error! Reference source not found.**.

Tab. 5.5

	Telcagepant	Rizatriptan	p-value
Per-attacks analysis			
Normal functional ability after 2 hours	279/384(72.7%)	228/320(71.3%)	0.742
Normal functional ability after 24 hours	373/384(97.1%)	298/320(93.1%)	0.020
Per-patient analysis			
MIDAS (1 month period)			
Baseline	7.9 ± 9.2	8.0 ± 7.6	
At 1 month	5.9 ± 9.8	6.0 ± 8.2	
At 2 months	6.7 ± 11.7	6.9 ± 9.2	0.752
At 3 months	6.8 ± 13.9	7.0 ± 8.5	

	Telcagepant	Rizatriptan	p-value
At 12 months	3.7 ± 4.6	4.0 ± 4.3	
MIDAS (3months period)			
At 3 months	10.5 ± 9.9	10.0 ± 9.1	0.901
At 6 months	11.6 ± 9.2	11.7 ± 9.4	0.979
Pain (0 - 10)			
At 3 months	5.2 ± 2.4	6.2 ± 2.9	0.366
At 6 months	5.2 ± 2.3	6.3 ± 2.1	0.244
Days with migraine			
At 3 months	11.9 ± 7.1	12.8 ± 5.1	0.736
At 6 months	11.5 ± 8.5	12.7 ± 7.6	0.725

The results were similar in both groups at 2 hour measures post treatment. At 24 hour measures, the differences were clearly in favor to telcagepant.

Differences at MIDAS between baseline and follow-up evaluation are reported in Table **Error! Reference source not found.**. The results were similar in both groups.

Monthly headache rates for migraine and non-migraine headaches by 3-month period intervals are shown in Figure 5..
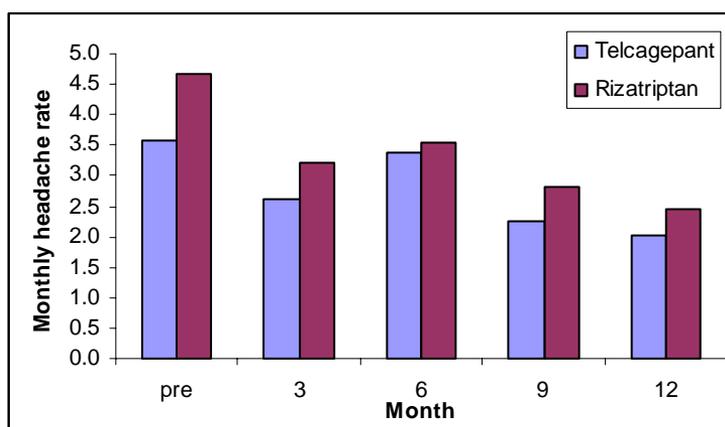

Fig. 5.5

In both treatment groups the monthly headache rate declined over time. The treatment groups appeared generally similar, although the headache rate tended to be numerically lower in the telcagepant group than in the rizatriptan group at most time intervals

Tolerability and Safety

Adverse events reported within 14 days of dosing are summarized in

Table **Error! Reference source not found.**.

	Telcagepant N=14	Rizatriptan N=10
One or more adverse event	6 (42.9%)	5 (50%)
Drug-related adverse event	4 (28.6%)	4 (40%)
Serious adverse events	0	0
Triptan related adverse event	3 (21.4%)	3 (30%)
Discontinuation because of adverse events	0	0
Common adverse events:		
Abdominal pain	1 (7.1%)	0
Asthenia	1 (7.1%)	2 (20%)
Dizziness	1 (7.1%)	1 (10%)
Dry mouth	2 (14.2%)	2 (20%)
Paresthesia	2 (14.2%)	2 (20%)
Dysuria	2 (14.2%)	0
Myalgia	1 (7.1%)	0
Upper respiratory tract infection	1 (7.1%)	1 (10%)
Hemorrhoids	1 (7.1%)	0

Tab. 5.6

Both telcagepant and rizatriptan were generally well-tolerated. However, fewer drug-related adverse events were reported for telcagepant vs rizatriptan. There were no serious laboratory adverse events and no discontinuations because of laboratory adverse events

Discussion

Our study supports the hypothesis that CGRP plays an important role in migraine pathogenesis and that oral CGRP receptor antagonists such as telcagepant are effective in long term treatment of migraine symptoms of headache, photophobia, phonophobia, and nausea, and also well-tollered.

A total of 384 attacks were treated with telcagepant and 320 with rizatriptan over a period of 12 months.

In the previous phase 3 trials [28] [20], the patients treated a single migraine attack. The efficacy rates for 2-hour pain freedom following telcagepant 300 mg were comparable in the 2 studies and was significantly more effective than placebo on all efficacy end points and comparable to that of zolmitriptan 5 mg.

In our study rizatriptan appeared numerically more effective than telcagepant for treating mild, moderate, or severe migraine attacks at 2 hours post dose. These numerical differences in efficacy were not sustained over time. At 2 hours post dose, telcagepant showed higher responder rates for absence of phonophobia, photophobia and nausea, and

comparable rates for 2- to 24-hour sustained pain freedom. In a post-hoc analysis of 2-hour pain freedom response by usual migraine treatment at baseline (triptan vs. non-triptan), rizatriptan showed numerically higher responder rates than telcagepant primarily in patients who administered triptans as their usual migraine treatment; the 2 treatment groups were more similar among patients who were non-triptan users. This finding suggests that the observed numerical efficacy advantage of rizatriptan at 2 hours may be limited to those patients who typically use triptans for their migraines. Both telcagepant and rizatriptan demonstrated a consistent treatment effect over time.

Telcagepant was well tolerated with an adverse experience profile similar to that of rizatriptan. Specific adverse experiences which were slightly less common for telcagepant 300 mg than rizatriptan in this study were abdominal pain, asthenia, dizziness, dry mouth, paresthesia, upper respiratory tract infection. No clinically relevant changes in laboratory measures, including transaminase levels, were seen although these were assessed up to 7 days or more after dosing.

The strength of this study is the temporal factor, that of observing the efficacy and tolerability over time. Another strength is the wide range of primary and secondary outcome parameters which were prespecified in the analysis and selected exploratory endpoints which included functional disability outcomes.

Functional outcomes clearly showed decreased impairment and improved quality of life scores with telcagepant and rizatriptan.

The treatment with telcagepant compared with rizatriptan resulted in statistically significant return to normal functional ability at 24 hour post dose; the results obtained at 2 hour were similar in both treatments. The measures of MIDAS score between baseline and follow-up evaluation at 1th, 2th ,3th,6th, 12th month after treatment didn't demostrate statistically significant differences in two groups. The number of days with headache and the average judgement on attack's severity (as defined in MIDAS) were similar at 3th and 6th month measures in the two groups.

There were no cardiovascular events in the present study but, although telcagepant is not a direct vasoconstrictor and in principle is therefore safe for use in patients with known vascular disease, such patients were excluded from the current trial.

Conclusions

Our data may suggest that CGRP receptor antagonists appear to be effective in the treatment of moderate and severe migraine attacks with reduction of migraine duration and potentially frequency over time. They

show efficacy regarding the pain freedom, improvement of associated symptoms and functional disability. In addition, they show a prolonged effect of action compared to the triptans. That may suggest not only less rebound headache but perhaps also a prophylactic possibility. Furthermore, only minor adverse effects were reported and no cardiovascular side effects could be seen so far. This is probably due to the absence of vasoconstrictor properties and it also suggests that vasoconstriction is not necessary to abort acute migraine attacks. This lack of direct vasoconstrictor activity may represent an important advantage over the triptans. Further development of drugs against the CGRP receptor will offer a new promising way of treatment.

Additional studies to investigate a higher number of patients and monitoring the effect of telcagepant up to 48 h post dose are needed to further evaluate these observations.

PERSONAL RESEARCH (II): ACETYLSALICYLIC ACID IN MIGRAINE WITH AURA PREVENTION. A RETROSPECTIVE STUDY

Introduction

Cortical spreading depression (CSD) underlies the mechanism of aura [29] and possibly activate trigeminal nociception triggering headache mechanisms as well [30]. The threshold for initiation of CSD presumably is lower in migraineurs than in the normal population [31].

During migraine attacks, platelet activation occurs with release of dense bodies content in cerebral circulation[31]. The possible high concentration of glutamate and aspartate in cerebrovascular bed may contribute to the initiation and propagation of CSD and aura.

Based on these considerations, theoretically any prophylactic treatment with antiaggregating agents may prevent the MA by inhibiting platelet dense bodies release.

Therefore, we questioned whether a treatment with Acetylsalicylic Acid, an antiplatelet drug that irreversibly inhibits platelet cyclooxygenase (COX)-1, the key step in the production of TXA2 from arachidonic acid (AA), may be useful in the prophylactic treatment of MA.

Possible options for MA prophylactic treatments

Release of glutamate from platelet and neurons may constitute an important step in triggering neuronal depolarization and the occurrence of auras. Hence drugs that potentially interfere with the impact of glutamate on hyperexcitable neurons may prevent MA attacks.

Another possible option for MA prophylactic treatment is to reduce the low threshold to platelet activation and aggregation in MA patients.

Rationale of this study

The aim of this study is to evaluate if Acetylsalicylic Acid, an antiplatelet drug that irreversibly inhibits platelet cyclooxygenase (COX)-1, the key step in the production of TXA2 from arachidonic acid (AA), may be useful in the prophylactic treatment of MA. ASA is known to be a potent anti-platelet aggregation drug [32]. Such activity has been shown to be primarily due to an irreversible block of cyclo-oxygenase activity [33] the enzyme which catalyzes the transformation of arachidonic acid into the cyclic endoperoxydes PGG2 and PGH2, intermediate products, in the production of the "aggregatory" thromboxane A2 [34, 35]. On the other hand, blockade by aspirin of endothelial cyclo-oxygenase activity results in lower production of prostacyclin, an "anti-aggregatory" agent. This "aspirin therapy dilemma" may be bypassed by using low doses of aspirin [36]. In the past some studies used ASA at low dose in the prophylaxis of migraine with controversial results [37,38,39,40].

Patients and methods

We retrospectively reviewed the charts of 203 (139 females and 64 males, age range 8-87 yrs, mean 34.2±12.74) patients suffering from MA according to the ICHD II criteria, attending to Turin University Headache Centre from 1988 to 2007.

95 subjects (46.8%) were treated with ASA at low dose, 108 (53.2%) with other prophylactic therapies normally used for migraine for a period that ranged from at least 4 months to 194 months.

ASA was administered at 300 mg daily for the first 4 months, and then reduced the dosage to 200 mg daily for a month and to100 mg/day for the remainder therapy period.

The primary objective of this study was to evaluate the efficacy and tolerability of Acetylsalicylic Acid for migraine with aura prophylaxis compared with other prophylactic therapies normally used for migraine in a real world clinical setting.

Patients' diaries reporting headache frequency, duration, intensity, disability, accompanying symptoms and duration of the aura were

evaluated before beginning the treatment and after the end of it. Depending on these parameters, it has been given a positive or negative judgment as regarding the response to treatments.

There were analyzed the attacks' frequency and the aura duration in the group of patients treated with ASA.

There were analyzed also the adverse events in the two groups.

Patients were selected according to the following criteria:

- history of migraine with aura and/or aura without migraine;
- attacks occurring at least once a month;
- no past or present diseases, and in particular no history of cerebral focal activation.

Statistical Analysis

Continuous data were shown as mean ± SD and categorical data as counts and percentages. Normally distributed variables were compared by Student's t test, whereas categorical variables were compared with the use of the $\chi 2$ test with Fisher's exact test or Yates' continuity correction when necessary. The differences pre-post ASA treatment were evaluated by using the Student's t test for paired samples. Data were collected and reviewed in Microsoft Excel and statistical analysis was performed with SPSS 16.0 (SPSS Inc., Chicago, IL, USA). All 2-tailed $P < 0.05$ were considered statistically significant.

Results

Eighty-four patients (88.4%) treated with ASA referred positive results, while only 64 patients (59.3%) who underwent other prophylactic treatments did ($p < 0.001$).

The attacks' frequency of patients treated with ASA decreased significantly from 3.83±1.57 pre-treatment to 1.38±0.87 after treatment ($p<0.001$). Aura duration was markedly reduced from 36.21±19.80 pre-treatment to 22.0±15.5 after-treatment ($p<0.001$). In 7 out of 95 (7.3%) MA totally disappeared. Only 11 out of 95 (11.5%) patients were completely unresponsive to treatment.

ASA was well-tolerated. Mild gastralgia in 17 out of 95 patients (17.9%) treated with ASA was the unique adverse event reported.

Discussion

On the basis of the data of our retrospective analysis ASA appeared more effective in the prophylactic treatment for MA than other prophylactic therapies normally used for migraine. ASA significantly

reduces attacks frequency and length of auras[41]. So, in our study, ASA seemed to act on the aura mechanism.

From experimental data regarding the triggering of MA it was demonstrated that changes in ion homeostasis, especially glutamate, produce cortical hypoperfusion through neural depolarization [16] and play a critical role in initiating and propagating SD. Glutamate is released in cerebral circulation from the dense bodies of the platelets, during migraine attacks, when platelet activation occurs causing a possible focal minute cerebral ischemia, events that may determine release of potassium and glutamate from glia and cortical neurons, and auras [42].

Thus, any drug that determines the inhibition of platelet activation and of the secretion of excitatory amino acids from dense granules in the cerebral circulation can be an useful strategy in the treatment of MA.

The fact that the patients in our study not only experienced a reduction in migraine aura, but also a significant reduction in migraine frequency, suggests that the inhibition of CSD-like events may subsequently prevent migraine headache.

Because there is now compelling evidence that CSD-like events that trigger aura, may be provoked by extensive glutamate release, treatment with agents that interfere with the pathophysiological chain of events that may cause its release, such as the antiplatelet agents, provides an important approach to manage patients with migraine with aura.

Conclusions.

ASA is a safe drug with minor possible side effects that can be routinely used when prophylactic treatment of MA is required.

Nevertheless, this is a retrospective study and should be interpreted with caution and in any case confirmed by prospective studies.

General conclusions
1. Migraine, a disease known from ancient times, is a complex neurobiological disorder.
2. Migraine is considered, a complex primary brain disorder that involves a cascade of events that lead to persistent and inappropriate activation of the trigeminovascular pain system.
3. Trigeminal vasoactive neuropeptides are release during migraine attacks as calcitonin-gene-related peptide (CGRP).
4. The cortical spreading depression (CSD), the underlying mechanism of aura, can lead to persistent activation of nociceptors innervating the meninges and thus trigger headache mechanisms.

5. Recent studies demonstrated that migraine is a disorder of brain excitability characterized by deficient regulation of the cortical excitatory/inhibitory balance, mechanisms that may create the conditions for ignition of CSD.
6. A potential mechanism of migraine prevention therapy is the inhibition of cortical spreading depression that activates trigeminovascular afferents.
7. Two main mediators have been demostrated to be involved in migraine pathophysiology, namely, 5-HT and CGRP, knowledge that have led to the development of agents effective in the acute treatment of migraine (triptans and gepants).
8. In our first study rizatriptan appeared numerically more effective than telcagepant for treating mild, moderate, or severe migraine attacks at 2 hours post dose, but these numerical differences in efficacy were not sustained over time.
9. At 2 hours post dose, telcagepant showed higher responder rates for absence of phonophobia, photophobia and nausea, and comparable rates for 2 - to 24 hour sustained pain freedom than rizatriptan.
10. The treatment with telcagepant compared with rizatriptan resulted in statistically significant return to normal functional ability at 24 hour post dose.
11. The strength of this study is the temporal factor, that of observing the efficacy and tolerability over time of telcagepant.
12. In our second study, ASA appeared more effective in the prophylactic treatment for MA than other prophylactic therapies normally used for migraine.
13. In our study, ASA seemed to act on the aura mechanism, by reducing attacks frequency and length of auras .
14. Acetylsalicilic acid is a safe drug with minor possible side effects that can be routinely used when prophylactic treatment of migrene with aura prevention is required.

Personal publications

1. Lidia Savi, **Mihaela-Bianca Anoaica**, Florica Popescu, Lorenzo Pinessi, *Low-dose of ASA in the Prophylaxis of Migraine with aura. A retrospective study*. Romanian Journal of Psichofharmacology, 4, 32-35, 2008
2. **Mihaela-Bianca Anoaica**, Florica Popescu, Paul - Gabriel Anoaica, *The efficacy of telcagepant for acute treatment of*

migraine and its effect on migraine associated disability. Romanian Journal of Psichofharmacology, 13, 36-44, 2013

3. **Mihaela-Bianca Anoaica**, P.G. Anoaica, Florica Popescu, *Acetylsalicylic Acid in migraine with aura prevention. A retrospective study.* Current Health Sciences Journal, 40(2), 126-128, 2014

4. I. Rainero, S. Gallone, E. Rubino, P. Ponzo, W. Valfre, E. Binello, P. Fenoglio, S. Gentile, **Mihaela-Bianca Anoaica**, M. Gasparini, L. Pinessi, *Haplotype Analysis Confirms the Association Between the HCRTR2 Gene and Cluster Headache*-Headache,48,1108-14,2008

References

[1]   Edmeads JJ. Neurol *What is migraine? Controversy and stalemate in migraine pathophysiology* 1991; 238: S2-5.

[2]   P.P. Humphrey, W. Feniuk, M.J. Perren, H.E. Connor, A.W. Oxford, L.H. Coates, and D. Butina. *GR43175, a selective agonist for the 5-HT1-like receptor in dog isolated saphenous vein*. 1988, Br.J.Pharmacol., 94, 1123–1132.

[3]   Headache Classification Subcommittee of the International Headache Society. *The International Classification of Headache Disorders: 2nd edition*. Cephalalgia 2004; 24 Suppl 1:9.

[4]   Charles A. *The evolution of a migraine attack - a review of recent evidence*. Headache 2013; 53:413.

[5]   Cutrer FM, Huerter K. *Migraine aura*. Neurologist 2007; 13:118.

[6]   Ophoff RA, Terwindt GM, Vergouwe MN, Vaneijk R, Oefner PJ, Hoffman SMG, Lamerdin JE, Mohrenweiser HW, Bulman DE, Ferrari M, Haan J, Lindhout D, Vanommen GJB, Hofker MH, Ferrari MD. & Frants RR. *Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca^{2+} channel gene CACNL1A4*. Cell 1996; Nov. 1;87(3): 543-52.

[7]   Saxena PR. Rev Contemp Pharmacother 1994; 5: 259-69.

[8]   Read SJ. & Parsons AA. In: Edvinsson L Ed *Migraine & headaches pathopysiology* London Martin Dunitz Ltd 1999.

[9]   Gulbenkian S, Cunha e Sá M, Pinto Barosso C. & Edvinsson L. In: Edvinsson L, Ed. *Migraine & headache pathophysiology* London Martin Duntitz Ltd 1999; 17-30.

[10] S.J. Tepper, A. Rapoport and F. Sheftell. *The pathophysiology of migraine*. 2001,Neurologist, 7, 279–286.

[11] D. Pietrobon and J. Striessnig. *Neurobiology of migraine*. 2003, at. Rev. Neurosci., 4, 386–398.

[12] Moskowitz MA. *Neurogenic inflammation in the pathophysiology*

and treatment of migraine Neurology 1993; Jun;43(6 Suppl. 3): S16-20.

[13] Olesen JJ. *A review of current drugs for migraine*. Neurol 1991; 238 Suppl. 1: S23-7.

[14] Shields KG, Goadsby PJ: *Propranolol modulates trigemino-vascular responses in thalamic ventro-postero-medial nucleus: a role in migraine?* Brain 2005, 128(Pt 1):86-97.

[15] Lance JW, Goadsby PJ: *Mechanism and Management of Headache*. 7th edition. Philadelphia: Elsevier Butterworth Heinemann; 2005.

[16] Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. *Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials*. Lancet. 2001;358:1668-1675.

[17] Dodick D, Lipton RB, Martin V, et al. *Consensus statement: cardiovascular safety profile of triptans (5-HT1B/1D agonists) in the acute treatment of migraine*. Headache 2004;44:414–425.

[18] Doods H, Arndt K, Rudolf K, Just S. *CGRP antagonists: unravelling the role of CGRP in migraine*. Trends Pharmacol Sci. 2007;28:580-587.

[19] Petersen KA, Birk S, Lassen LH, et al. *The CGRP antagonist, BIBN4096BS does not affect cerebral or systemic haemodynamics in healthy volunteers*. Cephalalgia 2005;25:139 –147.

[20] Ho TW, Ferrari MD, Dodick DW, et al. *Antimigraine efficacy and tolerability of the novel oral CGRP receptor antagonist MK-0974:A Phase III clinical trial versus placebo and zolmitriptan*. Headache 2008;48:S7-8.

[21] Ho AP, Dahlöf CG, Silberstein SD, et al. *Randomized, controlled, trial of telcagepant over four migraine attacks*. Cephalalgia. 2010; 30:1443-1457.

[22] Villalon, C. M, Centurion, D Valdivia, L. F,, de Vries, P., Saxena, P. R, (2003). *Migraine: pathophysiology, pharmacology, treatment and future trends*. Curr Vase Pharmacol 1, 71-84.

[23] Ho, T. W, Edvinsson, L., Goadsby, P. J. (2010). *CGRP and its receptors provide new insights into migraine pathophysiology*. Nat Rev Neurol 6, 573-582.

[24] Villalón, C. M., & Olesen, J. {2009}. *The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs*. Pharmacol Ther 124, 309-323.

[25] Ho, T. et al. (2007) *Efficacy and tolerability of a novel, oral CGRP antagonist, MK-0974, in the acute treatment of migraine: results from a Phase 2 randomized, controlled, clinical trial*. Headache 47,748–749.

[26] Olesen, J. et al. (2004) *Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine*. N.Engl. J. Med. 350, 1104–1110.

[27] **Mihaela-Bianca Anoaica**, Florica Popescu, Paul - Gabriel Anoaica, *The efficacy of telcagepant for acute treatment of migraine and its effect on migraine associated disability*, Romanian Journal of Psichofharmacology, 13, 36-44, 2013.

[28] Connor KM, Shapiro RE, Diener H-C, et al. *Randomized, controlled trial of telcagepant for the acute treatment of migraine*. Neurology. 2009;73:970-977.

[29] Lauritzen M: *Pathophysiology of the migraine aura. The spreading depression theory*. Brain 1994, 117(Pt 1):199–210.

[30] Moskowitz MA, Nozaki K, Kraig RP: *Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms*. J Neurosci 1993, 13(3):1167–1177.

[31] Welch KM: *Brain hyperexcitability: the basis for antiepileptic drugs in migraine prevention*. Headache 2005, 45(Suppl 1):S25– S32.

[32] O'Brien JR: *Effects of salicylates on human platelets*. Lancet I: 779-783, 1968 42.

[33] Moncada S, Vane JR: *Arachidonic acid metabolites and the inter-actions between platelets and blood-vessel walls*. N Engl J Med 300: 1142-1147, 1979.

[34] Moncada S, Vane JR: *Pharmacology and endogenous roles of prostaglandin endoperoxides thromboxane A2 and prostacyclin*. Pharmacol Rev 30: 293-331, 1979.

[35] Roth GJ, Stanford N, Majerus PW: *Acetylation of prostaglandin synthase by aspirin*. Proc Natl Acad Sci USA 72: 3073-3076, 1975.

[36] Pareti FI, D'Angelo A, Mannucci PM, Smith JB: *Platelets and the vessel wall: how much aspirin*. Lancet i: 371-372, 1980.

[37] Bensenor IM, Cook NR, Lee IM, Chown MJ, Hennekens CH, Buring JE. *Low-dose aspirin for migraine prophylaxis in women*. Cephalalgia. 2001;21:175-183.

[38] Buring JE, Peto R, Hennekens CH. *Low-dose aspirin for migraine prophylaxis*. JAMA. 1990; 264:1711-1713.

[39] Diener HC, Hartung E, Chrubasik J, et al. *A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study*. Cephalalgia. 2001; 21:120-128.

[40] Masel BE, Chesson AL, Peters BH, Levin HS, Alperin JB. *Platelet antagonists in migraine prophylaxis.A clinical trial using aspirin and dipyridamole*. Headache. 1980;20:13-.

[41] **Mihaela-Bianca Anoaica**, P.G. Anoaica, Florica Popescu, *Acetylsalicylic Acid in migraine with aura prevention. A retrospective study*, Current Health Sciences Journal, 40(2), 126-128, 2014.

[42] Montagna P, Sacquegna T, Cortelli P, Lugaresi E (1989) *Migraine as defect of brain oxidative metabolism: a hypothesis*. J Neurol 236:124–125.

Acronyms

5-HIAA	hydroxyindoleacetic acid
5-HT	serothonin
A11	dopaminergic hypothalamic nucleus
AA	arachidonic acid
ACh	acetylcholine
AEs	adverse effects
AM	adrenomedullin
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASA	Acetylsalicylic acid
Au	auditory cortex
BOLD fMRI	larger oxygen level dependent-functional magnetic resonance
BTX-A	botulinum toxin type A
CBF	cerebral blood flow
CGRP	calcitonin gene-related peptide
CLR	receptor-like receptor
CNS	central neural system
CSD	cortical spreading depression
CV	cardio-vascular
DC	direct current
EEG	electroencephalography
eNOS	endothelial nitric oxide synthase
FHM	Familial hemiplegic migraine
GABA	gamma-aminobutyric acid
GMP	guanosine monophosphate
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
iNOS	inducible nitric oxide synthase
Ins	insular cortex
LPO	lateral preoptic nucleus
LTG	lamotrigine
M1/M2	motor cortices areas
MA	migraine with aura
MAO	monoamine oxidase
MAPKs	mitogen-activated protein kinases
MCs	dural mast cells
MIDAS	Migraine Disability Assessment Score Questionnaire
MMA	middle meningeal artery
MMPs	matrix metalloproteinases
MO	migraine without aura
NCF	nucleus cuneiformis
NI	neurogenic inflammation
NKA	neurokinin A
NMDA	N-methyl D-aspartate
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NOS	nitric oxide synthase
NRM	midbrain dorsal raphe nucleus
NRM	midbrain dorsal raphe nucleus
PACAP	Pituitary adenylate cyclase activating polypeptides
PAG	ventrolateral periaqueductal grey
Pf	parafascicular thalamic nucleus
PFO	patent foramen ovale
PH	posterior hypothalamus
PKA	protein kinase A
Po	posterior thalamic nucleus
PPE	plasma protein extravasation
PtA	parietal association cortex;
RAMP	receptor activity-modifying protein
RCP	receptor component protein
RSA	retrosplenial cortex
RVM	rostral ventromedial medulla
S1/S2	primary and secondary somatosensory cortices areas
SD	spreading depression
SNRI	serotonin and noradrenalin reuptake inhibitor
SP	substance P
SPG	sphenopalatine ganglion
SpVC	spinal trigeminal nucleus
SSN	superior salivatory nucleus
SSRI	selective serotonin reuptake inhibitor
TCC	trigeminocervical complex
TG	trigeminal ganglion
TNC	trigeminal nucleus caudalis
TNF	tumor necrosis factor
TVS	trigeminal vascular system
TXA2	thromboxane A2
V1/V2	visual cortex
VIP	vasoactive intestinal peptide
vlPAG	ventrolateral periaqueductal gray matter
VPM	ventral posteromedial thalamic nucleus