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ORIGINAL COMMUNICATION

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Efficacy and tolerability of acetazolamide in migraine prophylaxis: A randomised placebo-controlled trial

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* The persons and institutions participating in the DIAMIG study (Efficacy and tolerability of acetazolamide in migraine prophylaxis: a randomised placebo-controlled trial) are listed in Appendix.

Abstract *Backgrounds* Familial hemiplegic migraine and episodic ataxia type 2 (EA2) are allelic disorders with distinct types of mutations in the *CACNA1A* gene. EA2 attacks are remarkably sensitive to acetazolamide, a carbonic anhydrase inhibitor. The effectiveness of acetazolamide in migraine prophylaxis is unknown. *Objectives* To evaluate the efficacy and the tolerability of acetazolamide in migraine prophylaxis. *Methods* We compared daily oral 500 mg acetazolamide and placebo in patients with migraine in a multicentre, double-blind, randomised trial of 12 weeks duration after a run-in period of 4 weeks without treatment. Frequency of attacks at the last trial period of 4 weeks was the primary efficacy criterion. Secondary efficacy criteria were the frequency of attacks per 4 weeks, the severity and duration of attacks, the number of hours with migraine as well as the number of responders with more than 50 % reduction in attack frequency. *Results* 53 patients had been enrolled when the study was prematurely stopped because of a high number of withdrawals (34 %), primarily linked to acetazolamide related side effects. Considering the primary and secondary efficacy criteria, among the 53 included patients (27 in the placebo group and 26 in the acetazolamide group), no difference between the 2 study groups could be demonstrated. The most frequent adverse events related to acetazolamide were paresthesias and asthenia. *Conclusions* In this trial, migraine sufferers poorly tolerated acetazolamide given in an oral dose of 500 mg daily. No obvious prophylactic beneficial effect of acetazolamide appeared on migraine attacks.

Key words migraine · prophylaxis · acetazolamide

Introduction

The first identified gene involved in migraine is CACNA1A that encodes the pore-forming alpha1A subunit of neuronal P/Q-type Ca2+ channels [1]. Missense mutations in CACNA1A gene have been identified in familial hemiplegic migraine (FHM), including all cases with cerebellar symptoms [2, 3, 4]. Interestingly, distinct types of mutations in the CACNA1A gene have been identified in two other autosomal dominant disorders: mutations leading to protein truncation in episodic ataxia type 2 (EA2) and small expansions of a CAG repeat in spinocerebellar ataxia type 6 (SCA6) [1, 5, 6]. Although EA2 and FHM attacks have different clinical features, their phenotype share some similarities: the young age of onset of attacks, the presence of headache during attacks, emotional stress reported as the most frequent triggering factor, the permanent usually mild ataxia or gaze-evoked nystagmus (present in 20 % of FHM families) [5, 7].

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Acetazolamide, a carbonic anhydrase inhibitor is remarkably effective in the prevention of EA2 attacks [8] and it also has a beneficial effect in the management of periodic paralysis, myotonia congenita and paramyotonia congenita, all due to ion channels defects [9], but its exact mechanisms of action remain unclear. A prophylactic beneficial effect of acetazolamide has also been reported in a few cases of FHM [10, 11]. Given the involvement of CACNA1A in both EA2 and FHM, it is of interest to study acetazolamide in FHM. However, FHM is rare and the frequency of attacks is usually low (one every two or three years), so that it would be extremely difficult to perform a controlled trial of acetazolamide in the prevention of hemiplegic migraine attacks. We therefore decided to conduct a randomised, placebo controlled study of acetazolamide in migraine in general.

Methods

This study followed the guidelines recommended for controlled trials of drugs in migraine and was conducted in 8 centers in France [12]. This study was approved by an independent French ethical committee (CCPPRB/241-97 Pitié-Salpêtrière).

Patients

The selection of patients (ages 18 to 65 years) was based on a history of migraine with and without aura defined according to the International Headache Society diagnostic criteria and present for more than one year [13]. Other entry criteria included a frequency of migraine of 2 to 8 per month, no more than 6 days per month of interval headache, an age of onset of migraine ≤ 50 years. Concomitant migraine prophylaxis had to be discontinued at least 6 weeks prior to the trial (3 months for flunarizine).

The following patients were excluded:

- patients who abused drugs for headache, alcohol or other reasons,
- patients who had depression (DSM-III criteria) or who took antidepressant or antipsychotic drugs,
- women of childbearing potential who did not use contraception,
- patients who were allergic to sulfamides or compounds similar to acetazolamide,
- patients who took medication that contained a carbonic anhydrase inhibitor or that may interfere with potassium or acid-base balances,
- patients who had a history of renal lithiasis, renal or hepatic insufficiency, hyperuricemia, diabetes or hypokalemia.

Patients were allowed to use their usual symptomatic treatment of acute attacks. However, aspirin in a dose greater than to 1 g daily was not allowed because of potential interaction with acetazolamide to produce metabolic acidosis [14]. Written, informed consent was obtained for each patient.

Trial design

This was a multicenter, double-blind, randomised trial of 12 weeks duration after a run-in period of 4 weeks without treatment, comparing two parallel groups of oral acetazolamide 500 mg daily and placebo. Since there is no established dose-effect relationship of acetazolamide in EA2 prophylaxis and since reported effective daily doses range from 125 to 750 mg, we chose an intermediary dose of 250 mg twice daily known to be pharmacologically active [15]. A dose reduction to 125 mg twice daily was possible for individuals (half tablet twice daily) when there were side effects. Each package of trial medication contained 3 boxes of 5 blisters of 14 placebo or acetazolamide tablets. Randomisation was performed centrally by fax. The pharmacist of each investigator center delivered treatment package according to the randomisation number. Patients were supplemented with potassium chloride only if hypokalema occurred. At the first visit, a complete blood chemistry (sodium, potassium, bicarbonate, creatinine, uric acid plasma concentrations, transaminase and gamma-glutamyl transpeptidase activities), blood count, and beta-HCG (in women of childbearing potential) were performed and were repeated every 4 weeks after randomisation. During the run-in baseline period, the patients were asked to record the frequency, duration and severity of attacks of migraine and interval headaches using a headache diary. At the second visit, patients who reported 2 to 8 migraine attacks during the run-in period and no more than 6 days of interval headache and who had no abnormalities on blood examinations were randomised to acetazolamide or placebo. Thereafter, patients were seen every 4 weeks until the end of the trial.

Evaluation of results

At each visit, patients were provided with a headache diary recording all migraine attacks with their exact date, duration in hours, severity on a four points verbal scale (3 = severe, 2 = moderate, 1 = mild, 0 = no pain) and presence of accompanying symptoms (nausea and/or vomiting, photophophia, phonophobia). The investigator checked diaries with the patients at each visit and reported all records in the trial book.

The primary efficacy criterion was the frequency of attacks at the last trial period of 4 weeks. Frequency of attacks per 4 weeks, severity of attacks, duration of attacks and number of hours with migraine at the last trial period of 4 weeks were secondary efficacy criteria. We also evaluated the number of responders with more than 50 % reduction in attack frequency at the last trial period of 4 weeks compared with the baseline period.

Adverse Events

Patients were interviewed about possible adverse events at each visit. Blood pressure was measured at each visit. A complete blood examination (blood chemistry and blood count) was performed every 4 weeks after randomisation (see above). Patient drop-out was defined as any premature interruption of the trial for an included subject.

Statistical Analysis

The sample calculation was based on the primary efficacy criterion (i. e. frequency of attacks at the last trial period of 4 weeks). The alternative hypothesis was that acetazolamide reduces by 40 % the number of migraine attacks compared with placebo. We estimated from literature data the mean of migraine attacks per month to be 4 in the placebo group with an estimated variance of 10. Given a type I error of 5 % and a type II error of 10 %, the calculated sample size was 90 patients per treatment group (total 180 patients).

Comparisons of continuous variables were performed using Student's t-test. Comparisons of categorical variables were performed using the chi square test or Fisher exact test when required. All tests were two-sided. The trial discontinuation was studied using a survival analysis. For patients who dropped-out of the double blind phase after at least 4 weeks after randomisation, the efficacy analysis was based on data from their last trial period. A trial discontinuation was considered here as an event, otherwise censoring was considered at the end of the study. Survival curves were derived from Kaplan-Meier estimates. The two groups of treatments were compared using the log-rank test. Statistical analyses were performed using the S-Plus statistical software (Mathsoft, Seattle, version 4.5).

Results

53 patients (27 in the placebo group and 26 in the acetazolamide (ACZ) group) were enrolled but the study was prematurely stopped because of a high number of withdrawals (figure 1). The two study groups were comparable in demographic characteristics, baseline blood pressure and for migraine history (table 1).

Efficacy

Among the 53 included patients, no difference between the two study groups appeared in the frequency of attacks at the last trial period of 4 weeks (table 2). There was no difference either for the duration of attacks, the severity of attacks, the severity of associated symptoms, the number of 50 % responders between the 2 groups for the last trial period of 4 weeks and for the attack frequency per 4 weeks of treatment trial (table 2).

Tolerability and adverse events

18 patients (34 %) dropped out after randomisation, 6 in the placebo group and 12 in the ACZ group ($p = 0.04$). Kaplan-Meier estimates of trial discontinuation-free survival according to treatment are shown in Fig. 2. The reasons for trial discontinuation were adverse events in 11 patients and non-compliance or withdrawal of consent in 7 patients (figure 1). The most frequent adverse event was paresthesias, reported in 21/26 patients (81 %) in the ACZ group and in 2/27 patients (7.4 %) in the placebo group. The second most frequent adverse event was fatigue, drowsiness or memory impairment, reported in 15/26 patients (58 %) in the ACZ group versus 4/27 patients (14.8 %) in the placebo group (table 3). Other reported adverse events are presented in table 4. There was no serious adverse event such as renal lithiasis or blood dyscrasia.

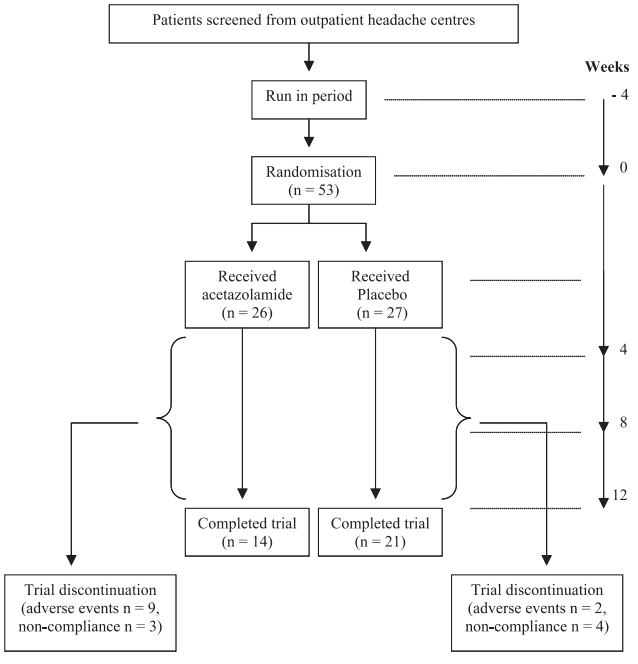

Fig. 1 Profile of the trial

Table 1 Baseline characteristics of patients

	Placebo group (n = 27)	ACZ group (n = 26)	P
Age (years)	38.5 [23–58]	40 [19–60]	NS
Gender (M/F)	8/19	5/21	NS
Weight (kg)	62.8 [44–90]	64.0 [43–112]	NS
Height (cm)	168 [153–186]	164 [146–182]	NS
Systolic blood pressure (mmHg)	121 [105–150]	123 [100–150]	NS
Diastolic blood pressure (mmHg)	76 [50–100]	79 [60–100]	NS
Migraine history:			
Migraine without aura	25	23	NS
Migraine with aura	2	3	NS
Age of onset (years)	18.6 [5–37]	20.2 [6–27]	NS
Attack frequency (per month)	5.2 [3–8]	4.7 [2–8]	NS
Attack duration (hours)	11.6 [1–96]	13 [0.2–138]	NS

Values are means with ranges in parentheses. (NS = not significant)

Table 2 Primary and secondary efficacy criteria at the last trial period of 4 weeks

	Placebo group	ACZ group	p values
Frequency of attacks per 4 weeks	3.5	4	NS
Duration of attacks (hours)	11.6 [1–96]	13 [0.16–138]	NS
Severity of attacks (scale from 1 to 3)	1.9	2	NS
Number of hours with migraine	138 [0–351]	124 [0–538]	NS
% of responders (> 50 % reduction in attack frequency)	32	31	NS

Values are means with ranges in parentheses. (NS = statistically not significant)

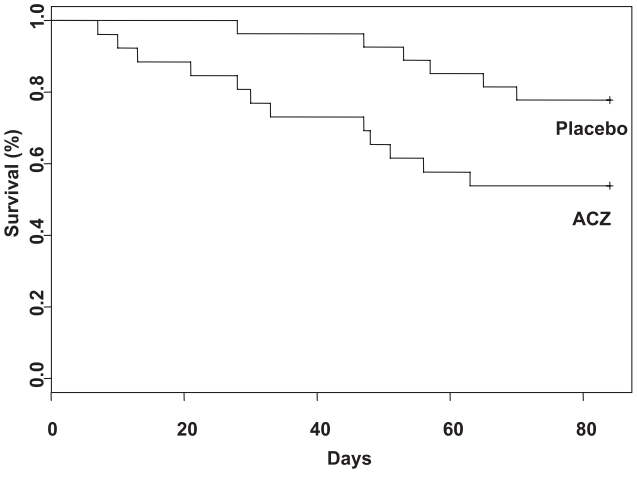

Fig. 2 Kaplan-Meier estimates of trial discontinuation-free survival according to treatment: logrank : p=0.04

Table 3 Adverse events

	Placebo group (n = 27)	ACZ group (n = 26)
Paresthesia	2 (7.4 %)	21 (81 %)
Fatigue, drowsiness, memory impairment, malaise, fasciculations	4 (14.8 %)	15 (58 %)
Gastrointestinal intolerance	2 (7.4 %)	3 (11.5 %)
Hypokalemia	0	1 (3.8 %)
Hyperuricemia	0	1 (3.8 %)
Skin eruption	2 (7.4 %)	0
Fever and shivering	1 (3.7 %)	0
Dry mouth	1 (3.7 %)	1 (3.8 %)
Breast tension	1 (3.7 %)	0
Rhinitis	2 (7.4 %)	1 (3.8 %)
Tinnitus	1 (3.7 %)	0
Miscellaneous	3 (11 %)	1 (3.8 %)
Total	**19**	**44**

Table 4 Bicarbonates monitoring per 4 weeks of trial

	Bicarbonates		
	Placebo	ACZ	p values
Baseline	28.6	27.9	NS
Week 4	30.9	22.8	0.008
Week 8	27.7	23.9	< 0.0001
Week 12	27.9	24.8	0.002

Values are means.

There was a significant difference in mean systolic blood pressure between the two groups but only for the first 4 weeks of trial period (119 mm Hg in the ACZ group, 128 mm Hg in the placebo group, p = 0.01). In the ACZ group, diastolic blood pressure showed a trend toward a decrease but the difference from placebo was not statistically significant (75 mmHg in the ACZ group and 81 mmHg in the placebo group at the first 4 weeks of trial period).

A significant decrease of bicarbonate plasma concentrations was noted in the ACZ group compared with the placebo group in each 4 weeks of trial period (table 4). However, there were no significant differences between the 2 study groups concerning potassium, creatinine, sodium, or uric acid serum levels, for any of the 4 weeks periods of the trial.

Discussion

This randomised placebo controlled trial mainly shows that acetazolamide given in an oral dose of 250 mg two times daily is poorly tolerated by migraine sufferers. Central nervous system (CNS)-related side effects including paresthesia and asthenia were reported by more than 80 % of patients and lead to trial discontinuation in 34 % of the patients. These side effects may be related to the metabolic action of acetazolamide since an early and significant decrease in plasma bicarbonate occurred in the ACZ group. Some degree of metabolic acidosis is expected with acetazolamide, which normally leads to an increase in urinary bicarbonate concentration and a decrease in the excretion of titratable acid and ammonia [15]. Excessive metabolic acidosis has been correlated with symptoms of fatigue in elderly glaucoma patients receiving acetazolamide [16]. The frequency of acetazolamide-related side effects in this trial contrasts sharply with the rare side effects reported in patients with acute mountain sickness or idiopathic intracranial hypertension treated with acetazolamide, a drug that considerably improves their headache [17, 18]. Acetazolamide related side effects are also infrequent in EA2 or in hypokalemic periodic paralysis except for renal lithiasis that may occur during long-term treatment [8, 9]. It is interesting to note that topiramate – an antiepileptic drugs that inhibits carbonic anhydrase – has also been evaluated in migraine prophylaxis with some efficacy in reduction of migraine frequency but with primarily CNS-related and dose related side effects including paresthesia, taste alteration, memory impairment, weight-loss, anorexia and dyspnea [19, 20]. These findings of poor tolerance of carbonic anhydrase inhibitors in migrainous subjects suggest a hypersensitivity to metabolic acidosis. This would be another example of the frequent "hypersensitivity" of migraine sufferers, illustrated for instance by their poor tolerance to dopaminergic agonists [21].

No firm conclusion can be drawn concerning the efficacy of acetazolamide in migraine prophylaxis as the study was prematurely stopped and therefore lacks power, given the intended number of subjects. However, among the 53 included patients, there was no tendency towards a beneficial effect of acetazolamide for any of the primary or secondary efficacy criteria. This study can not either answer the question whether migraine with aura may better respond to acetazolamide than migraine without aura since very few patients suffering migraine with aura were included (Table 1). However, the small sample size is probably not the only explanation for the apparent lack of efficacy of acetazolamide in migraine prophylaxis. It may also be that migraine in its usual variety (i. e. mostly without aura) responds to prophylactic treatment differently from FHM, and FHM from EA2. Interestingly, using magnetic resonance spectroscopy (MRS), abnormally elevated cerebellar intracellular pH has been demonstrated between attacks of EA2, returning to normal after acetazolamide administration [22]. MRS studies in migraine patients have failed to show abnormal intracellular pH even in prolonged attacks of migraine with aura or hemiplegic migraine [23, 24].

In conclusion this study mainly shows that acetazo-

lamide 500 mg daily is very poorly tolerated by migrainous subjects. Although the relatively small sample size does not allow firm conclusions about efficacy, acetazolamide did not seem to have a prophylactic effect. These results may not apply to FHM or to migraine with aura and they clearly contrast with the remarkable efficacy and tolerance of this drug in EA2.

Appendix

Trial Organisation and data management

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- Paris, Pharmacie Centrale des Hôpitaux: Blandine Lehmann, Annick Tibi.

Investigators

(The number of patients included are given in parentheses)

- Paris, Lariboisière Hospital: Service de Neurologie (20): Katayoun Vahedi (Principal Investigator), Richard Djomby, Mohammed El Amrani, Gina Lutz, Hélène Massiou and Marie-Germaine Bousser; Département de Diagnostic et de Traitement de la Douleur (3): Gérard Cunin.
- Strasbourg, Centre Hospitalier Régional et Universitaire, Service de Neurologie (8): Jean-Marie Warter.
- Paris, Cochin Hospital, Unité d'Évaluation et de Traitement de la Douleur (7): Dominique Valade.
- Toulouse, Rangueil Hospital, Service de Neurologie (5): Nelly Fabre.
- Paris, Laennec Hospital, Consultation Douleur (4): Stéphane Donnadieu, Pauline Boulan.
- Paris, Ambroise Paré Hospital, Consultation Douleur (4): Nadine Attal.
- Paris, Saint-Antoine Hospital, Centre d'Evaluation et de Traitement de la douleur (2): Annie Sergent, François Boureau.

Statistical analysis

- Paris, Necker Hospital, Service de Biostatistique et d'Informatique Médicale, Université Paris V: Pierre Taupin and Paul Landais.

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