Original Paper

Acetylsalicylic Acid in Migraine with Aura Prevention - a Retrospective Study

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ABSTRACT: In a retrospective study we evaluated the efficacy and tolerability of Acetylsalicylic Acid (ASA), an antiplatelet drug, in the prophylactic treatment of migraine with aura (MA). We reviewed the charts of 203 patients suffering from MA according to the ICHD II criteria, attending to Turin University Headache Centre. 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. 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 ($p<0.001$). ASA was well-tolerated. ASA is a safe drug with minor possible side effects that can be routinely used when prophylactic treatment of MA is required.

KEYWORDS: *Aura, Migraine, Acetylsalicylic Acid, Prophylaxis*

Introduction

Migraine with aura (MA) is a primary headache disorder that affects about 30% of migraine sufferers. The International Headache Society's (IHS) diagnostic criteria for MA [1] provide a clinical description of the aura, the disorder's most distinctive feature: aura consists of transient, unilateral or bilateral visual, sensory or motor symptoms considered to arise from a recurrent reversible, idiopathic dysfunction of the cortex or brainstem.

MA in the majority of cases is a relatively easy-to-diagnose form of headache, but when confronted with it, the real challenge is to select the most effective treatment.

The treatment of MA symptoms often represents a major clinical problem for headache specialists. MA usually is characterized by low frequency attacks: three o four attack/year, and does not need a prophylactic therapy [2]. However, in some patients the frequency of the auras attacks is higher, one or more in a months and, in others, the number of auras may increase from few to many attacks in a month or week. In such cases, prophylaxis of MA is justified after organic causes have been excluded.

Although vascular changes are no longer considered the primary cause of migraine headache, and the genesis of aura could be mainly linked to neuronal changes [3] due to the cortical spreading depression (SD) and changes in ion homeostasis, especially that of glutamate [4,5], resulting in cortical hypoperfusion through neuronal depolarisation in the cerebral cortex, platelets could probably still play an important role in MA pathogenesis. Platelets of migraine sufferers, in fact, present several functional anomalies regarding the content of granules and their secretion, adequately stimulated [6]. In particular, in comparison to healthy control subjects, higher levels of excitatory amino acids, such as glutamic and aspartic acids, are stored in dense bodies. During migraine attacks, platelet activation occurs with release of dense bodies content in cerebral circulation [5]. Release of glutamate may be essential in the initiation and propagation of spreading cortical depression and aura which some believe is central to the genesis of migraine attacks [8]. Based on these considerations, theoretically any prophylactic treatment with anti-aggregation agents may prevent the MA by inhibiting platelet dense bodies release.

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 [9-12]. Such activity has been shown in vitro to be primarily due to an irreversible block of cyclo-oxygenase activity [11-14] the enzyme which catalyzes the transformation of arachidonic acid into the cyclic endoperoxydes PGG2 and PGH2,

DOI: 10.12865/CHSJ.40.02.08

intermediate products, in the production of the "aggregatory" thromboxane A2 [15]. The irreversibility of the aspirin effect is consequent on the anuclear platelet incapability of enzyme re-synthesis [16]. On the other hand, blockade by aspirin of endothelial cyclo-oxygenase activity results in lower production of prostacyclin, an "anti-aggregatory" agent [17]. This "aspirin therapy dilemma" may be bypassed by using low doses of aspirin [18-21]. Low doses of aspirin have been reported to inhibit in vitro only platelet cyclo-oxygenase activity and to result in reduced formation of salicylate, which is known to disturb aspirin antiaggregatory effects [22]. It is to be stressed that data emphasize lack of aspirin efficacy in women following administration of high doses of aspirin [23].

In the past some studies used ASA at low dose in the prophylaxis of MA with controversial results [24-26].

Methods

We reviewed the charts of 203 (139 females and 64 males, age range 8-87 yrs, mean 34.2±12.74 STD) 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.

Patients taking ASA began with a dosage of 300 mg/day for minimum 4 months, and then reduced the dosage to 200 and 100 mg/day.

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.

Headache frequency, duration, intensity, disability, accompanying symptoms, duration and intensity 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 analysed 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.

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 categoric variables were compared with the use of the χ^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.

Conclusions and discussion

On the basis of the data of this 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.

SD is considered the pathophysiological mechanism that underlies the MA. Glutamate play a critical role in initiating and propagating SD. It is released in cerebral circulation from the dense bodies of the platelets, during migraine attacks, when platelet activation occurs. Thus, any drug that determine 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.

Our study clearly suggests that it is possible to prevent MA attacks with agents that interfere with the pathophysiological chain of events that may trigger the aura, such as the antiplatelet agents, ASA in this specific case.

So, we conclude that 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.

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 DOI: 10.12865/CHSJ.40.02.08