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Tolerance study among Filipinos on acetylsalicylic acid and dipyridamole

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Abstract

Objective: To document the frequency, severity and pattern of occurrence of the headaches among Filipinos taking acetylsalicylic acid plus dipyridamole. *Methods:* Open non-comparative study carried out among 105 Filipinos, 18 years old or above with transient ischaemic attack or completed stroke within past three months. Patients with history of peptic ulcer disease, gastrointestinal bleeding or hypersensitivity to study drugs were excluded. Subjects were given 25mg of acetylsalicylic acid and 200mg of dipyridamole twice a day for 2 weeks. Number of dropouts due to headache was the primary outcome measure. Incidence, severity, duration and timing of headaches and the need for an analgesic were documented in patients' diary. Evaluation was done after 7 and 14 days of treatment. *Results:* One hundred and five patients were recruited. The mean age was 56 years, 65% were males and 94% was diagnosed as stroke. Seventy patients (67%) experienced headache, mostly mild to moderate and disappearing during the second week of treatment. Twenty-two patients dropped out during the study with 17 patients (16%) dropping out due to headache.
Conclusion: Around 70% of Filipino subjects taking acetylsalicylic acid and dipyridamole experienced headache during treatment, mostly mild to moderate and disappearing after one week of treatment. One out of 6 patients discontinued treatment due to headache.

INTRODUCTION

The European Stroke Prevention Study 2 (ESPS 2) has shown that the combination of low dose acetylsalicylic acid 25 mg and dipyridamole 200mg, in a modified-release form, both given twice daily was more effective than either agent prescribed singly in the secondary prevention of ischaemic strokes.[1] Data from the 6,602 patients studied for 2 years indicated that stroke risk when compared to placebo was reduced by 18% with acetylsalicylic acid alone, 16% with dipyridamole alone and 37% with the combination therapy. Based on current evidences, the Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy stated that " aspirin combined with extended-release dipyridamole (25/200 mg BID) is more effective than aspirin alone (50 to 325 mg QID)"[2] in the prevention of stroke among patients experiencing non-cardioembolic cerebral ischaemic events.

Filipino neurologists however, are concerned with giving high doses of dipyridamole due to the headaches experienced by some of their patients. The headache from dipyridamole is probably related to its vasodilator effect.[3] However, there is no documentation of the frequency, severity and pattern of occurrence of these headaches as reported by Filipino patients taking high doses of dipyridamole.

In the ESPS 2 study done among Caucasians, headache was the most common adverse event occurring approximately 15% higher with the dipyridamole-treated patients as compared to placebo. Also headache and gastrointestinal events predominated as a reason for early discontinuation of treatment in patients receiving a dipyridamole-containing regimen. A recent open study of acetylsalicylic acid and dipyridamole by 36 healthy volunteers[4] showed that 67% of the volunteers reported episodes of headache during the first day of treatment, but reducing rapidly in the 12 days study period.

This study was done to document the frequency, severity and pattern of headache experienced by Filipino patients given

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combination of acetylsalicylic acid and dipyridamole in order for physicians to assess practicability of high-dose dipyridamole in the secondary prevention of stroke.

METHODS

Patients were included into the study if they: (a) were 18 years or above; (b) experienced transient ischaemic attack or completed ischaemic stroke within preceding three months and (c) signed informed consent. Patients were excluded from the study if they had any of the following: (a) recent history of peptic ulcer disease or other gastrointestinal bleeding and (b) hypersensitivity or intolerance to study drugs.

The design of the study was an open non-comparative study. Patients meeting inclusion and exclusion criteria were given 25mg acetylsalicylic acid and 200mg of dipyridamole (Aggrenox®) twice a day for 14 days. Before entering the trial, patients were informed of the following statement: "The treatment that your physician is prescribing in order to prevent you from having another transient ischaemic attack or stroke may cause headache during the first few days of treatment. This is a known effect of treatment and is not in itself harmful. If you do get headache, please try to continue the treatment regularly as the headache will pass as you get used to the medicine. If the headache is uncomfortable you may take a pain-killing medicine together with your stroke prevention medicine. At any point of the study, if there are adverse reactions or intolerable headaches please report them to your doctor for advise for treatment and withdrawal from the study."

The frequency and severity of headache were monitored daily during the 14-day study period using a patients' diary. During clinic visits after 7 day and 14 day treatment, occurrence of headaches was elicited both through spontaneous reporting and systemic inquiry asking the following questions: Did you experience headache since the last visit?; (b) If yes, how severe was it? (mild = awareness of a sign or symptom which is easily tolerated; moderate = discomfort enough to cause interference with usual activity; severe = incapacitating with inability to do work or usual activity); (c) Did you have to discontinue the medication? or (d) Was it relieved by intake of analgesics?

Based on reported conservative estimate of prevalence of headaches of 65% among volunteers taking acetylsalicylic acid and dipyridamole and using 10% precision rate, the sample size calculated was around 100 patients.

Descriptive statistics was used to document frequency of headaches and their classification by severity.

RESULTS

One hundred and five patients with mean age of 56 years participated in the study. Sixty five percent were male. Baseline characteristics of patients included in the study are shown in Table 1.

A total of 70 patients (67%) experienced headache during the two week study period with 67 patients (64%) experiencing headaches during the first week of treatment but only 17 patients (16%) having headaches in the 2nd week (Figure 1). As shown, majority of the patients experienced only a mild to moderate headache. Fifty percent of patients complained of headaches on Day 1. There was a decreasing trend such that by the end of treatment period (Day 14), headache incidence was only 3%.

A total of 22 patients dropped out during the study (Table 2) with 17 patients (16%) dropping out due to headache. A composite profile of the frequency and severity of the headache of the 17 patients who dropped out due to headache is shown in Figure 2.

Fourteen of the 17 patients who dropped out did so during the first week and 3 during the second week of study. There were 83 patients who completed the study with a ratio of 1 out of 6 quitting the study because of headache.

A total of 28 patients (27%) took analgesics at anytime during the study period. Sixteen patients out of the 83 who completed the study took analgesic for the headache. Of these, only one patient needed to take analgesic during the 2nd week of treatment. Twelve patients out of 17 that dropped out of the study took analgesics.

There were no differences in the baseline characteristics of patients who did and did not experience headache during the 2-week study period. There were 20 patients who experienced 30 other adverse events; most of these were mild (Table 3).

DISCUSSION

The antiplatelet drugs, acetylsalicylic acid and dipyridamole have long been used in clinical practice in the secondary prevention of stroke. Acetylsalicylic acid inactivates the platelet enzyme cyclooxygenase, subsequently inhibits

Table 1. Characteristics of study patients (N=105)

Mean age (s.d.) in years	56 (11)
Sex, percentage of male: female	65 : 35
Mean weight (s.d.) in kg	62 (9.6)
Diagnosis	
Transient ischaemic attack	6%
Stroke	94%

Figure 1: Composite profile of the frequency and severity of headache among the 70 patients who experienced headache during the 14-day treatment period

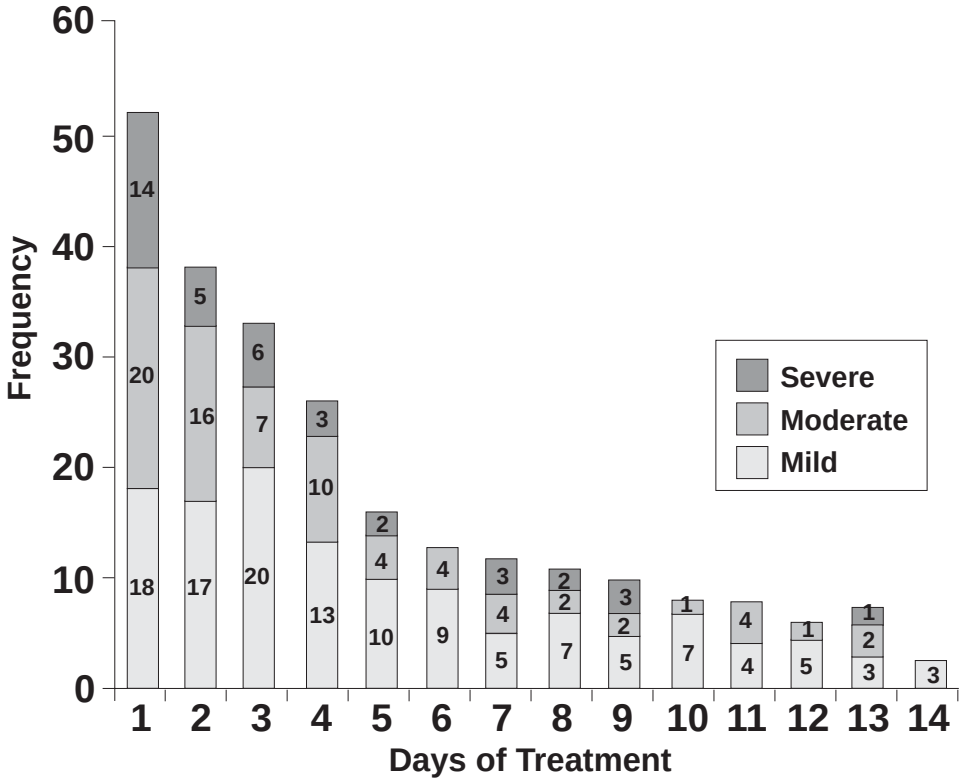

Table 2. Frequency of patients who dropped out of acetylsalicylic acid and dipyridamole and the reasons (N=105)

	Number of patients (%)
Number of drop out	22 (21)
Reasons for drop out	
Headache	17 (16)
Recurrence of weakness	1 (1)
Gastritis	1 (1)
Hypoglycemia	1 (1)
Shortness of breath	1 (1)
General body weakness	1 (1)

Figure 2: Composite profile of the frequency and severity of headache of the 17 patients who experienced headache and eventually dropped out from the study

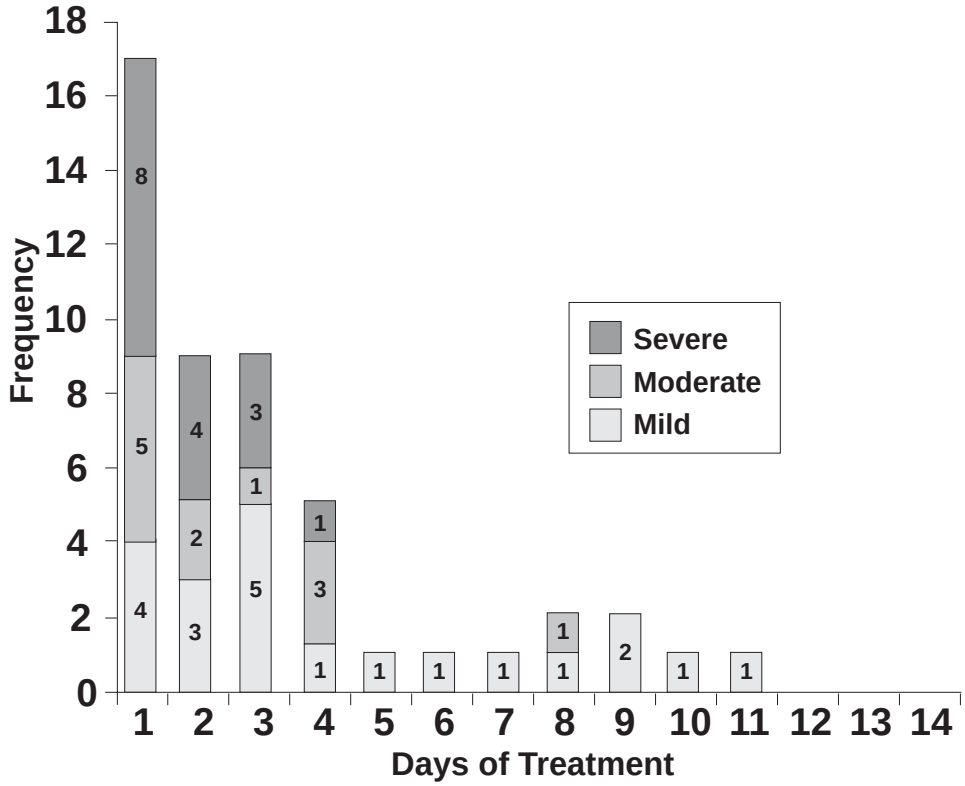

Table 3. Adverse events other than headache experienced by 20 patients

Adverse events	Frequency
Gastric or epigastric pain	5
Vomiting	4
Diarrhea	4
Dizziness	4
General weakness	2
Sleepiness	2
Abdominal pain	2
Shortness of breath	2
Nape pain	1
Discomfort of shoulder joint and back	1
Pain in the leg/arm	1
Nose bleeding	1
Inability to sleep	1

thromboxane formation, which is a potent vasoconstrictor, while dipyridamole increases the concentration of cyclic AMP by inhibiting phosphodiesterase.

More recently, the European Stroke Prevention Study 2 (ESPS 2) has shown that the combination of low dose acetylsalicylic acid and dipyridamole was more effective than either agent alone.[1] Among the adverse events, dizziness and headache were the two most common reported respectively. In ESPS 2, headache developed in 38% of patients taking acetylsalicylic acid and dipyridamole, and about 8% of those taking the drugs had to discontinue therapy primarily because of headache.

In the ESPS 1 trial, headache associated with dipyridamole developed in 20.8% of patients.[5] This study however is marred by a large drop-out rate (45%) precluding the making of a reliable conclusion.

In our study, 67% of patients experienced headache during the 2-week treatment period. This prevalence rate is higher compared to ESPS 2 and ESPS 1 trials. We attribute this to the fact that the study was an open trial and the patients were instructed to document the incidence, frequency and severity of headache. Our study population had a high level of awareness and expectancy of this adverse event while on treatment. On the other hand, the patients in the ESPS 2 and ESPS 1 trials were blinded and were not informed that headache may occur during the course of treatment.

Theis et al[4] reported a study to look at the prevalence of headache in 36 healthy volunteers who were on acetylsalicylic acid and dipyridamole. The drug was given for two periods of 5 days each separated by 72 hours washout period. The study revealed a 67% prevalence of headache on Day 1 rapidly declining to 3% at the end of the study period. During the first day of treatment, majority of the headaches were described as mild or transient. In addition, peak incidence of headache tends to occur 2-3 hours after administration of the extended release formulation coinciding with the peak plasma concentration of dipyridamole.

The results of our study are very similar to that by Theis et al showing rapid development of tolerance to dipyridamole associated headache. Thus, while dipyridamole is associated with increase in headache, these headaches were mostly tolerable and resolved rapidly with time. This implies that if patients are properly informed and warned, this may reduce withdrawal and increase the compliance to acetylsalicylic acid and dipyridamole treatment.

In conclusion, although around 70% of Filipinos taking acetylsalicylic acid and dipyridamole experienced headache during the 2-week treatment period, these headaches were mostly mild to moderate and disappeared during second week of treatment. Approximately only 1 out every 6 patients who took acetylsalicylic acid and dipyridamole dropped out due to headache.

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