Clopidogrel as prophylactic treatment for migraine: A pilot randomised controlled study

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Structured abstract (141 words)

Introduction Anecdotal reports suggest that clopidogrel may prevent migraine attacks. We undertook a pilot randomised trial.

Method We randomised consecutive migraineurs with 4-15 headache days per 28 day month to receive clopidogrel 75 mg or placebo daily for 3 months. Headache was primarily assessed with a headache diary.

Results There were no statistically significant treatment effects. The number of headache days fell by 1.9 on clopidogrel and 1.6 on placebo (adjusted difference 0.02, CI -2.07 to 2.12). Headache severity rose by 0.14 points (out of 10) on clopidogrel, and fell by 0.63 on placebo; treatment effect 0.7 points (CI -0.11 to 1.57). The main treatment effect did not depend on the presence or absence of migraine with aura at baseline, a PFO or atrial septal aneurysm.

Discussion The evidence is inconclusive, but a multicentre trial would be feasible recruiting from primary care.

Key words: Migraine Clopidogrel

Introduction

There is evidence linking migraine with abnormalities of platelet morphology or function.[1] There is also a biologically plausible link between platelet aggregation and patent foramen ovale (PFO) or atrial septal aneurysm and migraine.[2]

Clopidogrel inhibits platelet aggregation and may improve migraine induced or worsened after device closure of a PFO for stroke or decompression illness.[3] Small non-randomised trials also suggest a benefit when migraine is the primary reason for closure[4,5] but the only randomised trial was negative.[6] Clopidogrel is given early after closure and this raises the possibility that it, rather than the mechanical closure, is effective against migraine.

We therefore designed a pilot randomised placebo-controlled trial of clopidogrel in consecutive patients with migraine.

Methods

Participants We recruited participants with migraine with or without aura as defined by International Headache Criteria who were aged 18 - 80 and had 4-15 headaches days in a 28 day month. Exclusions included high risk features suggesting cerebral pathology, contraindications to clopidogrel treatment, abnormal platelet or liver function at the first visit. Participants were recruited from the neurology outpatient department at Guy's or King's Hospitals or clinics run by general practitioners with a special interest in headache. The study was approved by the Guy's Ethics Committee (Reference 07-H0804-139) and was registered with the required bodies (EudraCT 2008-001604-23, MREC number CCT-NAPN-17625, ISRCTN35114412, UKCRN ID 4758, CTA number 11387/0002/001-0001, Community R and D reference RD LSLBB 458/2).

Design This was a randomised placebo-controlled parallel trial. There was a run-in period of a 28 day month on usual medication during which time a baseline headache diary was completed. At visit 2, patients with 4-15 headache days and no exclusion criteria were randomised to placebo or clopidogrel 75 mg once daily. Treatment lasted 3 months and a further headache diary was kept during the final 28 day month. All other medication including migraine prophylaxis and acute

treatment for attacks continued unchanged. Participants were questioned at visit 1 for their memory of bruising, rashes and indigestion and at visit 2 for these potential adverse events occurring during run-in. These questions were to establish whether reported adverse events at visit 3 and 4 whilst on study treatment represent a change from back-ground. At the first and last visits, the Headache Impact Test (HIT)-6 and Migraine Disability Assessment Score (MIDAS) questionnaires were completed.

Assessment of headache using the diary The participant recorded the times of the beginning and end of the aura and headache on a paper sheet with 28 spaces for each day of a calendar month. For calculating the number of headache days, a day was taken as the 24 hour period from the onset of the headache or aura. The severity was scored using a 10 point scale. If there was a range in the severity given for one day, the worst score was used. For days with no headache, a severity score of zero was used. For timing duration the headache was assumed to last all night if present at bed-time and still present on waking. If the headache was present at bed-time but absent on awakening, it was assumed to have ended at 23.00.

Adverse events Minor bruising and occasional indigestion were not counted as adverse events. Minor adverse events were defined as: frequent (more than daily) or severe bruising (bruises with a diameter larger than 3 cm); minor self-limiting nose bleed; minor heart-burn requiring no more than ad hoc antacids; minor skin rash; nausea or diarrhoea. Major adverse events did not occur.

Echocardiography A full transthoracic study with a bubble contrast study was performed during the three months of the study but at no set time-point. The full echocardiographic methodology has been published elsewhere.[7] A patent foramen ovale (PFO) was classified according to the number of microcavitations crossing to the left within ≤3 cardiac cycles; a moderate or large PFO was taken as > 20 microcavitations. An atrial septal aneurysm was defined by a base > 10 mm wide and an apex moving by ≥ 10 mm between left and right atria.

Randomisation A 1:1 randomisation sequence (to A and B) was prepared electronically (PS) and the meaning of A and B was determined by someone not involved with the

study. The study was therefore triple-blind (participant, research team and prescribing pharmacist). The placebo and active treatment were supplied in identical tablets in blister packs within cardboard packs numbered sequentially. The packs were prescribed in sequential order.

Statistical analysis The primary end-point was change in headache days using the headache diary. Secondary end-points were the duration and severity of attacks using the headache diary. Summaries are presented as means (SD), median (quartiles) or n (%) as appropriate. Differences between groups were estimated using linear regression, adjusting for baseline measures in each case. Robust standard errors were used to allow for unequal variance between groups. Headache duration (as recorded by diary, a secondary endpoint) was normally distributed only after log transformation. The analysis of headache duration is based on logs calculated after adding 0.5 to remove zeros; the results presented as the percentage change due to randomised treatment in the corresponding average value. Results for the primary outcome were compared by presence or absence of aura at baseline, presence or absence of a moderate or large PFO and presence or absence of atrial septal aneurysm. Interaction tests (using Wald's method) were carried out in the whole sample to look for differences in treatment effect between these subgroups.

Power calculations using the actual numbers of subjects recruited[8] showed 48% power to detect a difference of two headache days due to treatment, 82% for three days, and 97% for four days. Statistical analysis was carried out in Stata version 11.2 (StataCorp, College Station, Texas). Results are reported according to the CONSORT guidelines.

Results

The target sample was not reached before completion of the grant because of slow recruitment as most patients had headaches that were too frequent (>15 headache days per month) to be eligible for the study. Between 14 May 2009 and 28 June 2012 we approached 98 potentially suitable patients. There were 18 excluded for reasons given in Figure 1. Therefore 80 were randomised and these were well matched for age, gender, headache characteristics, education, alcohol and smoking, family history of migraine and stroke and results of baseline questionnaires (Table 1).

Effect on headache

There was no statistically significant treatment effect. The number of headache days (the primary endpoint) fell by 1.9 days on clopidogrel and 1.8 days on placebo (adjusted difference 0.02; CI -2.07 to 2.12). The number of headaches over 3 months from the MIDAS questionnaire fell by 12.5 on clopidogrel and 5.6 on placebo (adjusted difference -3.69; CI -12.18 to 4.81). The HIT-6 score fell by 1.8 on clopidogrel and by 3.1 on placebo (adjusted difference 1.20; CI -0.97 to 3.37). Mean headache severity rose by 0.14 points with clopidogrel, and fell by 0.63 points with placebo (adjusted difference 0.7; CI -0.11 to 1.57).

Average headache duration was 26% (CI -22% to 103%) longer on randomised treatment.

Subgroup analysis

Interaction tests showed no evidence of a difference in treatment effect whether the participant reported aura at baseline, or whether a PFO or atrial septal aneurysm was present or absent. Rates of aura fell from 38% (13/34) to 32% (11/34) in the clopidogrel group and from 29% (10/34) to 16% (5/31) in the placebo group; the adjusted risk difference was 12.1% (-6.6 to 30.7). There were no significant treatment effects for the primary outcome in any of the defined subgroups. In participants with aura there was a fall of -1.6 headache days on clopidogrel, and -0.9 on placebo (treatment effect -0.67, CI -3.22 to 1.87), compared to falls of -2.3 and -3.9 in patients without aura (treatment effect (+1.65, CI -1.96 to 1.87)

In patients with a PFO, there was a fall of -1.3 headache days on clopidogrel compared with -4.1 on placebo (difference 2.2; CI -2.1 to 6.6). For those with no PFO the fall on clopidogrel was -2.1 compared with -0.6 on placebo (difference -1.5; CI -3.9 to 0.9). For those with an atrial septal aneurysm, the fall was -1.0 on clopidogrel compared with -4.6 on placebo (difference 3.6; CI –3.6 to 10.7) and in those without an atrial septal aneurysm the fall was -2.0 on clopidogrel compared with -1.3 on placebo (difference -0.6 (CI -2.8 to 1.7).

Adverse events

The adverse events were all minor and similar for placebo (21 events reported for 14 subjects) and clopidogrel (29 events for 17 subjects). There were 3 bruises reported on placebo and 5 on clopidogrel. There was one nose bleed reported on placebo and 3 on clopidogrel. There was indigestion in two participants on placebo and none on clopidogrel.

Discussion

This study was adequately powered for a difference of three or more headache days per month between clopidogrel and placebo, but the number of headache days in a calendar month fell by only 1.9 on clopidogrel and by 1.8 on placebo. Using the MIDAS questionnaire, the number of headaches in 3 months fell by 12.5 on clopidogrel and by 5.6 on placebo.

Comparison with the literature

There is no previously published randomised controlled trial of clopidogrel versus placebo, but one study shows that aspirin is no more effective than placebo[9] and another that it is less effective than metoprolol.[10]

The evidence for a potential therapeutic effect for clopidogrel therefore remains anecdotal or circumstantial. Device closure for stroke or decompression disease may occasionally induce or worsen migraine[3] for which clopidogrel has then been found to be effective.[3] Small non-randomised trials of PFO closure also suggest a benefit when migraine is the primary reason for closure.[4,5] Clopidogrel is always given early after closure raising the possibility that the drug rather than the device is the effective agent. However we showed no interaction between the presence or absence of PFO or atrial septal aneurysm and clopidogrel.

Migraine is unlikely to be a unitary condition and headache is more likely to be a final common pathway for a variety of different processes. Until we are better able to characterise migraineurs, it may still be worth a therapeutic trial of clopidogrel in an individual migraineur if other agents fail.

Conclusion

There was no evidence that clopidogrel is either more or less effective than placebo for the prophylaxis of migraine. However a multicentre trial would be feasible preferably recruiting from a larger population base, probably in primary care.

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Figure legends

Figure 1. CONSORT Diagram

The miscellaneous reasons for exclusion were abnormal liver function tests (n=1), meningitis (n=1), and opted for a new intravenous therapy for migraine (n=1).