*Platelets*, March 2006; 17(2): 100–104

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**ORIGINAL ARTICLE**

# Effect of aspirin, clopidogrel and dipyridamole on soluble markers of vascular function in normal volunteers and patients with prior ischaemic stroke

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*(Received 6 June 2005; revised 16 June 2005; accepted 17 June 2005)*

**Abstract**
Although the mechanisms of action by which aspirin, clopidogrel and dipyridamole inhibit platelets are well characterised, their effects on soluble modulators of thrombosis, inflammation, and endothelial function have yet to assessed systematically. In this investigation aspirin (A), clopidogrel (C), and dipyridamole (D) were administered singly and in combination (A, C, D, AC, AD, CD, ACD) in random order for 2 weeks (without washout) to 11 healthy subjects and 11 patients with previous ischaemic stroke. At the end of each treatment period plasma cyclic guanosine monophosphate (cGMP), monocyte chemoattractant pertide-1 (MCP-1), nitric oxide metabolites ($NO_x$), plasminogen activator inhibitor-1 (PAI-1) and von Willebrand factor (vWf); and serum C-reactive protein (CRP) and platelet derived growth factor (PDGF); were measured blinded to treatment. Dipyridamole reduced plasma vWf levels (%) in both volunteers, −10.0 (4.95), and patients, −10.11 (4.34) ($p < 0.05$). Dipyridamole also lowered CRP (mg/l) in patients, −0.96 (0.47), but not volunteers. Clopidogrel reduced PAI-1 (ng/ml) in volunteers, −5.30 (2.20) ($p < 0.05$), and patients, −3.61 (2.75) (non-significant trend). Aspirin lowered PDGF (ng/ml) in volunteers, −3.46 (1.55), but not patients. Triple antiplatelet therapy was superior to dual and mono therapy in reducing vWf levels. In conclusion, antiplatelet agents have non-platelet-related effects on soluble modulators of thrombosis, inflammation, and endothelial function. In particular, dipyridamole reduces plasma vWf and clopidogrel lowers plasma PAI-1 levels. These effects may explain, in part, their roles in preventing atherothrombogenesis.

**Keywords:** *Aspirin, clopidogrel, dipyridamole, leucocyte, platelet, stroke*

## Introduction

The three antiplatelet agents, aspirin, clopidogrel and dipyridamole, are widely used for secondary stroke prevention on the basis of results from large trials and systematic reviews [1, 2]. Whilst their antiplatelet actions are well described, their effects on other vascular cells and soluble factors are less well defined.

Platelets, leucocytes, and endothelial cells contribute to the pathogenesis of vascular disease [3] through direct cell–cell interactions and the release of atherothrombogenic factors. Platelets release several cytokines including platelet-derived growth factor (PDGF), platelet factor 4 and CD40 ligand, each of which has been linked to the inflammation and coagulation pathways [4–6]. Similarly, monocytes and macrophages generate cytokines including macrophage chemoattractant protein-1 (MCP-1), a chemokine important during atherogenesis [7], and interleukin-6 (IL-6) [8], a procoagulant and stimulator of hepatic synthesis of C-reactive protein (CRP); CRP amplifies inflammatory and procoagulant responses [9, 10]. IL-6 also increases endothelial production of the fibrinolytic inhibitor, plasminogen activator inhibitor type 1 (PAI-1) [3, 11]. Endothelial cells also release von Willebrand factor (vWf), which facilitates platelet and thrombus adhesion to endothelium [12], and nitric oxide (NO), a potent vasorelaxant, antiplatelet and antileucocyte agent [13] whose effects are mediated by the second messenger cyclic guanosine monophosphate (cGMP) [14].

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ISSN 0953–7104 print/ISSN 1369–1635 online 
DOI: 10.1080/09537100500235966

We assessed the effects of aspirin, clopidogrel and dipyridamole on a panel of the above soluble markers of vascular function in normal volunteers and patients with a prior history of ischaemic stroke. We also assessed the effect of combining the three antiplatelet agents on the soluble markers since we have shown previously that three drugs may be superior to one or two in inhibiting platelet function in vitro [15].

## Methods

### *Design*

Two randomised, outcome-blinded, multiway, crossover trials of antiplatelet therapy were performed in normal volunteers and patients with prior ischaemic stroke. The study design has been published previously [16] in a report of the effect of aspirin, clopidogrel and dipyridamole on the function of circulating platelets, phagocytes and their conjugates.

### *Subjects*

The study protocol was approved by the local Research Ethics Committee. All subjects gave written informed consent and the trials were performed according to the Declaration of Helsinki and the principles of Good Clinical Practice. Eleven healthy volunteers without any history of vascular disease were recruited from hospital or university staff or their friends. Eleven stable patients with a prior history of ischaemic stroke (on clinical and neuroimaging criteria) within 5 years were recruited from the stroke service at Nottingham City Hospital [16]; each patient was receiving aspirin for vascular prophylaxis. Subjects were excluded if they had a history of cerebral haemorrhage, gastrointestinal bleeding, peptic ulcer, anaemia, thrombocytopenia, any severe concomitant medical condition, or hypersensitivity or intolerance to any of the study drugs; were taking anticoagulation or a non-steroidal anti-inflammatory drug; had a blood pressure >180/110 mmHg; or were pregnant or lactating women.

### *Interventions*

All subjects received 2-week periods of open-label aspirin (A, 75 mg daily), clopidogrel (C, 75 mg daily) or modified release dipyridamole (D, 200 mg twice daily). The drugs were given either singly (A, C, or D), in pairs (AC, AD, or CD) or all three together (ACD) in random order [16]. Normal volunteers, but not patients, were also studied off all therapy. No washout periods were used since the length of each treatment phase (14 days) exceeded the lifespan of platelets (~10 days). Randomisation was performed using a computer and the treatment codes held by the hospital's Pharmacy to ensure concealment of allocation. Blood samples were collected at the end of each 2-week treatment phase. Adverse events are reported previously [16]. Subjects who withdrew from treatment were replaced to ensure that complete data were present for each person; laboratory data from withdrawing subjects are not included in the statistical analyses.

### *Laboratory study*

Serum and plasma collected into 3.8% sodium citrate (1 : 9 volume) or 4.0 mmol/l EDTA were centrifuged ($1500 \times g$ for 15 min) within 1 h of venepuncture. Aliquots were frozen at $-80^{\circ}$C and then assayed in batches using commercially available ELISA kits. CRP (Kalon Biological, Hants, UK) and PDGF (R&D System, Abington, UK) were measured in serum; cGMP (R&D System), vWf (Corgenix, Cambridgeshire, UK), MCP-1 (R&D System) and PAI-1 (Technoclone TC, Surrey, UK) were analysed in citrated plasma.

Plasma (citrated) nitric oxide ($NO_x$) levels were determined from measurement of its stable end products, nitrate and nitrite, by the method of chemiluminescence (Sievers 280 Nitric Oxide Analyser, Analytix Limited, County Durham, UK) [17]. This involved injecting 10 µl of deproteinised plasma samples into vanadium chloride [18]. The nitrate and nitrite present in samples were reduced to NO, and quantified from a calibration curve based on prepared concentrations of sodium nitrate.

### *Statistical analysis*

The primary analysis compared the presence and absence of each drug on soluble markers, i.e. aspirin versus no aspirin, clopidogrel versus no clopidogrel, and dipyridamole versus no dipyridamole. Secondary analyses compared triple therapy (ACD) versus all other drugs, as before [16]. Analyses were performed using the SAS statistical package.

## Results

Demographic and clinical information for the subjects are given in Table I. The stroke patients are representative of our clinical stroke service and were older and had more risk factors (more smokers, higher blood pressure and cholesterol) than the volunteers.

When considering the individual effects of the three antiplatelet agents on soluble markers of vascular function, three observations were made. First, dipyridamole significantly reduced plasma vWf levels in both volunteers and stroke patients (Table II). Second, dipyridamole reduced serum CRP

in patients but not volunteers (where a non-significant increase was present). Third, clopidogrel reduced plasma PAI-1 concentrations in volunteers (significant) and patients (non-significant trend). Fourth, aspirin reduced serum PDGF levels in volunteers but not patients. The three antiplatelet agents did not appear to alter MCP-1, $NO_x$ or cGMP levels in either subject group.

Patients had significantly lower levels of plasma $NO_x$ (difference 0.37, SD 0.17, $p < 0.001$) and higher levels of plasma vWf (difference −43.1, SD 39.5, $p = 0.019$) than volunteers (Table III); no differences in the other biomarkers were apparent. The use of triple antiplatelet therapy was not superior to mono or dual therapy with the exception that the combination of all three agents was associated with lower levels of plasma vWf than dual aspirin and clopidogrel in both volunteers and patients (Table III), a finding compatible with the above observation that dipyridamole lowers vWf levels.

Table I. Baseline characteristics of subjects. Mean (standard deviation) or frequency (%).

| | Normal volunteers | Previous ischaemic stroke |
|---|---|---|
| Number | 11 | 11 |
| Mean age (years) | 39 (8) | 62 (10) |
| Gender, male (%) | 8 (73) | 6 (55) |
| Hypertension (%) | 0 (0) | 8 (73) |
| Diabetes mellitus (%) | 0 (0) | 0 (0) |
| Smoking (%) | | |
| Never | 9 (82) | 3 (27) |
| Past | 1 (9) | 5 (45) |
| Current | 1 (9) | 3 (27) |
| Blood pressure (mmHg) | | |
| Systolic | 130 (14) | 150 (20) |
| Diastolic | 85 (4) | 86 (8) |
| Platelet count ($\times 10^9$ l) | 257 (35) | 282 (71) |
| Total cholesterol (mmol l$^{-1}$) | 5.0 (0.7) | 5.9 (0.8) |
| LDL-C (mmol l$^{-1}$) | 3.4 (0.6) | 3.8 (0.8) |
| HDL-C (mmol l$^{-1}$) | 1.0 (0.2) | 1.4 (0.4) |
| Triglycerides (mmol l$^{-1}$) | 1.3 (0.5) | 2.2 (1.5) |

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

## Discussion

These studies show that antiplatelet agents may alter soluble markers of vascular function. In particular, dipyridamole significantly reduced plasma vWf levels in both volunteers and patients with previous stroke, an effect seen previously in an independent study involving patients with ischaemic heart disease [19].

Studies in vitro and ex vivo have found that dipyridamole significantly reduces platelet adhesion to vascular sub-endothelium although the mechanism remains unclear [20, 21]. Both vWf and P-selectin are stored in Weibel-Palade body in the endothelium [22, 23]. Pro-inflammatory mediators activate cells causing Weibel-Palade bodies to fuse with the cell membrane resulting in the release of vWf and surface exposure of P-selectin. vWf and P-selectin are the primary molecules involved with platelet interaction with endothelium [23, 24]. In the present study we provide evidence that the inhibitory effect of dipyridamole on platelet adhesion may be mediated in part through inhibition of vWf release from endothelial cells.

Dipyridamole also appeared to lower serum CRP levels, a previously unreported finding. However, this finding was only present in patients with prior cerebrovascular disease and could simply reflect chance. Several studies have reported that dipyridamole potentiates nitric oxide-induced vasodilator activity through inhibiting phosphodiesterase V activity and thereby enhancing intracellular cGMP levels [25–27]. However, we did not observe changes in plasma $NO_x$ and cGMP levels with dipyridamole.

Clopidogrel showed an inhibitory effect on plasma PAI-1 levels (significant in volunteers, non-significant in patients) but not on other biomarkers. The reduction of PAI-1 has been observed in two earlier studies [28, 29] and may be achieved partially through inhibition of platelet activity [30, 31]. Previous studies have reported that clopidogrel lowers CRP levels in patients with acute vascular disease [32–34]. However, we did not confirm this observation, perhaps because CRP is an acute phase

Table II. Effect of aspirin (A), clopidogrel (C) and dipyridamole (D) on soluble markers; mean difference (standard deviation).

| | cGMP (nM) | CRP (mg l$^{-1}$) | MCP-1 (pg ml$^{-1}$) | $NO_x$ (μmol l$^{-1}$) | PAI-1 (ng ml$^{-1}$) | PDGF (ng ml$^{-1}$) | vWf (%) |
|---|---|---|---|---|---|---|---|
| Volunteers | | | | | | | |
| A *vs.* no A | 0.30 (0.43) | 0.52 (1.05) | 9.59 (15.97) | −0.06 (0.05) | 0.73 (2.20) | **−3.46 (1.55)** | 3.48 (4.95) |
| C *vs.* no C | −0.27 (0.43) | −0.64 (1.05) | 4.45 (15.97) | 0.02 (0.05) | **−5.30 (2.20)** | −1.89 (1.55) | 3.16 (4.95) |
| D *vs.* no D | −0.55 (0.43) | 0.23 (1.05) | 1.21 (15.97) | −0.001 (0.05) | −0.10 (2.20) | 1.70 (1.55) | **−10.01 (4.95)** |
| Patients | | | | | | | |
| A *vs.* no A | 0.39 (0.57) | 0.06 (0.47) | 9.02 (10.50) | −0.04 (0.06) | −3.77 (2.75) | 0.44 (1.98) | 2.90 (4.34) |
| C *vs.* no C | 0.59 (0.57) | 0.05 (0.47) | 16.97 (10.50) | 0.04 (0.06) | −3.61 (2.75) | 0.72 (1.98) | 1.88 (4.34) |
| D *vs.* no D | −0.28 (0.57) | **−0.96 (0.47)** | −0.64 (10.50) | −0.03 (0.06) | 0.42 (2.75) | −0.71 (1.98) | **−10.11 (4.34)** |

cGMP, cyclic guanylate monophosphate; CRP, c-reactive protein; MCP-1, macrophage chemoattractant peptide; $NO_x$, nitric oxide metabolites; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; vWf, von Willebrand factor; $p < 0.05$ in bold.

Table III. Effect of aspirin (A), clopidogrel (C) and dipyridamole (D) on soluble markers in normal volunteers and patients with previous ischaemic stroke: mean (standard deviation).

| | A | C | D | AC | AD | CD | ACD |
|---|---|---|---|---|---|---|---|
| Volunteers | | | | | | | |
| cGMP (nmol $l^{-1}$) | 2.9 (3.4) | 1.6 (1.3) | 2.5 (2.1) | 3.2 (2.8) | 1.8 (2.0) | 2.1 (2.5) | 1.7 (1.7) |
| CRP (mg $l^{-1}$) | 3.7 (6.3) | 2.5 (2.8) | 4.0 (6.5) | 2.3 (2.0) | 2.3 (2.8) | 1.5 (1.0) | 4.4 (6.9) |
| MCP-1 (pg $ml^{-1}$) | 242 (123) | 211 (81) | 240 (115) | 260 (137) | 249 (102) | 247 (107) | 242 (90) |
| NOx (μmol $l^{-1}$)) | 0.72 (0.17) | 0.95 (0.42) | 0.83 (0.28) | 0.83 (0.31) | 0.91 (0.24) | 0.81 (0.25) | 0.77 (0.19) |
| PAI-1 (ng $ml^{-1}$) | 32.1 (17.9) | 25.2 (19.1) | 29.7 (21.6) | 23.4 (14.8) | 27.8 (15.6) | 24.4 (11.5) | 25.3 (13.9) |
| PDGF (ng $ml^{-1}$) | 21.5 (11.3) | 23.8 (14.8) | 25.6 (13.1) | 20.8 (17.0) | 24.4 (18.0) | 23.9 (17.1) | 18.8 (12.7) |
| vWf (%) | 47.3 (46.4) | 56.3 (35.0) | 42.2 (18.4) | 62.2 (37.7)* | 53.7 (29.6) | 44.2 (31.8) | 40.9 (18.8) |
| Patients | | | | | | | |
| cGMP (nmol $l^{-1}$) | 2.6 (3.4) | 2.6 (2.9) | 1.3 (1.9) | 2.0 (3.2) | 1.9 (2.4) | 2.2 (2.5) | 3.2 (2.8) |
| CRP (mg $l^{-1}$) | 4.3 (4.6) | 4.3 (3.1) | 2.9 (2.6) | 3.6 (2.2) | 3.3 (2.6) | 3.3 (2.9) | 2.9 (2.3) |
| MCP-1 (pg $ml^{-1}$) | 181 (49) | 202 (54) | 175 (49) | 205 (43) | 202 (61) | 195 (42) | 210 (49) |
| NOx (μmol $l^{-1}$) | 0.35 (0.16)** | 0.38 (0.25) | 0.34 (0.21) | 0.36 (0.29) | 0.28 (0.18) | 0.38 (0.41) | 0.34 (0.27) |
| PAI-1 (ng $ml^{-1}$) | 36.7 (19.6) | 34.3 (14.6) | 37.8 (20.2) | 29.5 (19.8) | 32.8 (20.6) | 35.5 (16.6) | 29.5 (13.3) |
| PDGF (ng $ml^{-1}$) | 22.8 (17.8) | 21.7 (18.1) | 22.0 (15.9) | 22.7 (18.5) | 19.9 (11.3) | 21.5 (19.1) | 23.3 (13.3) |
| vWf (%) | 90.4 (31.0)** | 89.9 (38.4) | 81.6 (32.3) | 96.7 (41.1)* | 84.5 (36.8) | 83.2 (46.2) | 79.7 (31.0) |

cGMP, cyclic guanylate monophosphate; CRP, c-reactive protein; MCP-1, macrophage chemoattractant peptide; $NO_x$, nitric oxide metabolites; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; vWf, von Willebrand factor. *$p < 0.05$ ACD versus other therapies, **$p < 0.05$ volunteers versus patients.

protein and is elevated significantly in acute rather than chronic vascular disease.

Aspirin reduced serum PDGF levels but only in volunteers; this finding has not been reported before and might reflect chance. A reduction in CRP with aspirin was found in an earlier study of patients with hypertension [35] but not in studies involving healthy subjects [36, 37]. Apart from differences in subjects, this positive study involved prolonged treatment over 18 weeks, whereas aspirin was given for shorter periods (<1 month) in the above two neutral studies and ours.

We found, in secondary analyses, that plasma $NO_x$ levels were lower, and vWf levels higher, in patients with cerebrovascular disease than in volunteers. Both factors are produced by endothelial cells and the results support previous finding that endothelial dysfunction is present in patients with vascular disease. For example, patients with hypertension, hypercholesterolaemia, diabetes mellitus and previous clinical vascular events have lower $NO_x$ and elevated vWf levels [38, 39]. Similarly, acute stroke is associated with low $NO_x$ and high vWf levels [18, 40].

Although our trials were small, we used a cross-over design (thereby allowing each subject to act as their own control) which considerably increases statistical power as compared with a parallel group design. Additionally, we assessed the effects of antiplatelet agents in two different sets of subjects which increases the external validity of the findings. Importantly, measurements were made by one person who was blinded to treatment.

In summary, dipyridamole reduced plasma vWf levels, a measure of endothelial dysfunction, in both normal subjects and patients with previous ischaemic stroke. Similarly, clopidogrel lowered plasma PAI-1 concentrations in both sets of subjects (significantly so in volunteers). The findings suggest that these agents have additional effects on non-platelet aspects of atherothrombogenesis, mechanisms which may explain, in part, their roles in preventing recurrent vascular events such as stroke.

## Acknowledgements

We thank the volunteers and patients who took part in the study. PB is Stroke Association Professor of Stroke Medicine; the Division of Stroke Medicine receives core funding from The Stroke Association.

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