

## SCIENTIFIC LETTERS

### Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement

Following coronary stent placement, platelet activation is a major determinant of the risk of subacute stent thrombosis.<sup>1</sup> Combined antiplatelet treatment with ticlopidine and aspirin reduced platelet activation after coronary stenting.<sup>1</sup> Although combined antiplatelet treatment consisting of aspirin and ticlopidine has significantly reduced early ischaemic events following coronary stenting, stent thrombosis still occurs in up to 1% of treated patients, especially in the early days after the intervention, probably because of delayed onset of action of ticlopidine. Clopidogrel is a ticlopidine-like novel thienopyridine inhibitor of ADP induced platelet activation.<sup>2</sup> Clopidogrel differs from ticlopidine in that it has a favourable safety profile compared to ticlopidine and reveals an accelerated antiplatelet activity after first administration. The present study sought to investigate the antiplatelet effect of various doses of clopidogrel in patients undergoing coronary stent placement; comparison was made with standard ticlopidine treatment.

Thirty patients were randomised into three treatment arms: group I (n = 10), ticlopidine 2 × 500 mg as loading dose and 2 × 250 mg daily thereafter; group II (n = 10), clopidogrel 1 × 300 mg loading dose and 1 × 75 mg per day; or group III (n = 10), clopidogrel 1 × 600 mg plus 2 × 75 mg daily thereafter. All patients received aspirin 2 × 100 mg per day concomitantly. Peripheral venous blood samples were taken with a loose tourniquet through a short venous catheter inserted into a forearm vein before and then 2, 4, 24, and 48 hours after first administration of anti-

platelet medication. Platelet aggregation in response to ADP (5 or 20 µmol/l) and to TRAP (25 µmol/l) was evaluated by optical aggregometry in citrated blood samples,<sup>3</sup> and ATP release as marker for dense granule secretion was determined by luminometry.<sup>3</sup> Surface expression of P-selectin (CD 62P binding) was analysed by flow cytometry according to published methods and served as index of degranulation of α-granules.<sup>3</sup>

Compared to baseline values ADP (20 µmol/l) induced platelet aggregation was inhibited significantly by approximately 55–59% (p < 0.01) within the first 4 hours after drug administration in patients receiving the 600 mg loading dose (fig 1). Substantially less inhibition of ADP (20 µmol/l) induced aggregation (38–40%) was found in patients receiving an initial loading dose of clopidogrel of 300 mg compared to the patient group treated initially with 600 mg (p < 0.01) (fig 1). No substantial platelet inhibition within the early hours after drug administration was observed in patients treated with ticlopidine (fig 1). Inhibition of ADP (20 µmol/l) induced platelet aggregation further decreased after 48 hours in patients receiving 300 mg clopidogrel (up to 52%), whereas in patients treated with 600 mg clopidogrel platelet aggregation remained on the level of inhibition found during the first few hours after drug administration (fig 1). In patients treated with ticlopidine, ADP (20 µmol/l) induced platelet aggregation started to be substantially inhibited by approximately 38% at 48 hours (p < 0.01) (fig 1). Similar results were obtained for all three groups of patients when a weaker stimulus of platelet aggregation was applied (ADP 5 µM) (data not shown).

When the thrombin related activating peptide (TRAP), a strong agonist of platelet aggregation, was used to stimulate platelets, only weak inhibition of platelet aggregation was observed in all three patient groups throughout the observation time. Inhibition of TRAP (25 µM) induced platelet aggregation at 2 hours and 48 hours was 11% and 8%, respectively, (p < 0.05) in the group treated with 600 mg clopidogrel, and 5% and

9% (p < 0.05), respectively, in the group treated with 300 mg clopidogrel. In patients receiving ticlopidine, TRAP induced aggregation tended to be slightly decreased by 5% after 2 hours or 48 hours; however, this did not reach a significant level (data not shown).

A substantial decrease of ADP (20 µM) induced α-degranulation, as evaluated by the surface expression of P-selectin (CD62P), was exclusively found in patients treated with 600 mg clopidogrel loading dose. The median (25% and 75% quartile) of the mean intensity of immunofluorescence (MIF) of CD62P was 244 (231, 261) before and 207 (183, 223) 48 hours after administration (p < 0.05) (data not shown). In the group treated with 300 mg clopidogrel or with ticlopidine no substantially inhibitory effect on α-degranulation was seen throughout the observation time (data not shown). Furthermore, in none of the treatment groups was TRAP (25 µM) induced α-degranulation substantially inhibited (not shown). In none of the groups of patients was substantial inhibition of ADP (5 and 20 µM) or TRAP (25 µM) induced ATP release found (data not shown).

The present study shows that a combined antiplatelet treatment with aspirin and clopidogrel in a high loading dose of 600 mg and a continuous dose of 150 mg per day is superior to the combination of aspirin and standard clopidogrel (300 mg loading dose plus 75 mg per day)<sup>4</sup> or ticlopidine (2 × 500 mg loading dose plus 2 × 250 mg per day) treatment<sup>1</sup> in suppressing platelet aggregation after coronary stenting. Administration of 600 mg clopidogrel accelerates inhibition of ADP induced platelet aggregation during the first few hours to a level that cannot be accomplished by the conventional dosing regimen of 300 mg clopidogrel<sup>4</sup> before 48 hours after first drug administration. The accelerated effect of 600 mg clopidogrel narrows the therapeutic gap of ticlopidine and might be beneficial, especially for high risk patients treated with coronary stenting. The study shows furthermore that clopidogrel in a high loading dose of 600 mg is able to reduce the degranulation of α-granules. Since platelet release products derived from α-granules are mitogenic, it is possible that the combination of aspirin and clopidogrel in a high dosage might modulate platelet dependent restenotic processes following coronary angioplasty. On the other hand, the lack of inhibition of aggregation and degranulation of TRAP stimulated platelets in all three treatment groups indicates that even combined antiplatelet treatment with aspirin and clopidogrel cannot substantially reduce platelet activation in an environment of high thrombin activity. This might be of importance in patients with acute coronary syndromes or who are being treated by fibrinolysis for acute myocardial infarction. It is tempting to speculate that in these patients the addition of further antithrombotic compounds including glycoprotein IIb/IIIa blockers and antithrombins to aspirin and clopidogrel might favour a better clinical outcome.

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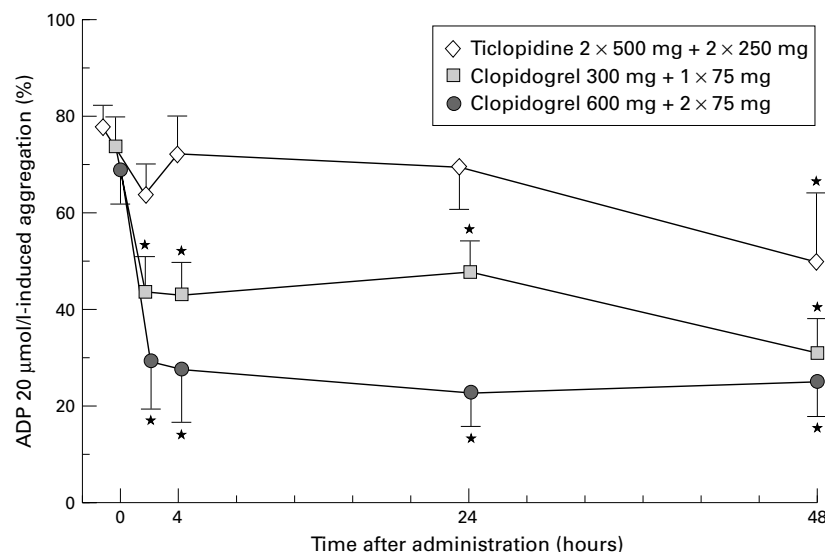


Figure 1 Effect of high loading dose of clopidogrel on ADP induced platelet aggregation. Patients were randomised into three treatment arms: ticlopidine 2 × 500 mg plus 2 × 250 mg daily thereafter (n = 10); clopidogrel 300 mg loading dose plus 1 × 75 mg daily (n = 10); and clopidogrel 600 mg loading dose plus 2 × 75 mg daily thereafter (n = 10). All patients received aspirin 2 × 100 mg/day concomitantly. Platelet aggregation was studied after stimulation with ADP (20 µmol/l) by light transmittance aggregometry in citrated platelet rich plasma. \*Significant difference (p < 0.05) compared to starting concentrations.

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### Management of severe heart failure by specialist palliative care

A large number of patients die from heart failure. While a small proportion of deaths in severe heart failure are sudden, the majority will die from worsening heart failure or a comorbid condition. A retrospective study of patients with heart disease in the UK, and a prospective study of heart failure in the USA, showed that a high proportion of patients had uncontrolled symptoms at the end of life.<sup>1,2</sup> In addition there was evidence of communication problems between health care professionals and patients and their carers, in particular, open communication about dying and patients' preferences about how and where they should be cared for.<sup>3</sup> Significant communication problems as well as unmet psychosocial needs have also been identified in a prospective study.<sup>4</sup>

Specialist palliative care has traditionally offered a multiprofessional approach to manage such problems in patients with cancer and more recently motor neurone disease and AIDS. Its potential role in improving care for patients with heart failure at the end of life has been recognised in strategic plans for health care in the UK.<sup>5</sup> Nevertheless there is very limited information about the management of heart failure patients by specialist palliative care. We conducted a retrospective study of the needs and service use of heart failure referrals to specialist palliative care.

St Christopher's Hospice is a specialist palliative care unit in London with 62 inpatient beds and over 450 community patients covering a population of 1.75 million. Since 1994 referrals of patients with heart disease have been accepted. We identified these cases from a comprehensive database of all referrals between 1994 and 1999 and reviewed the case notes.

Twenty seven patients were referred because of heart failure out of a total of 9920. The mean age of heart failure patients was 73 years (range 48-98 years). Fifteen referrals were made from primary care, 5 from a hospital palliative care team, 5 from a hospital doctor, and 2 from a non-St Christopher's community palliative care team. Four patients died before assessment (delay 1-4 days). Four patients were not accepted (2 were inappropriate on assessment and required help from psychiatric and social services, 1 was out of area, and for 1 there were inadequate data).

Thus 19 patients were assessed and managed by the hospice. Eleven patients had

significant comorbidity. The most common symptoms reported as severe on initial assessment were weakness (11 patients), breathlessness (6), drowsiness (5), anorexia (5), dry mouth (3) and weight loss (3).

The non-physical needs recognised on initial assessment were adjustment of the patient and family to dying (7 patients), exhaustion of carers (5), psychological distress of the family (5), communication and relationship problems between patient and family or carers (4), adjustment difficulties of the family associated with fear of loss and guilt (4), anxiety and frustration of patient (3), and miscellaneous spiritual, financial, and insight issues.

The specialist palliative care team delivered care both in the community and as hospice day and inpatients. It provided help with recognition and management of psychological distress of family or carers (7 patients), discontinuing unnecessary cardiac and non-cardiac drugs (7), early bereavement follow up of family or carers at risk (7), mobilising increased nursing, social or financial support (4), and appropriate medication required for terminal care (4). Adjustments to cardiac medication were made in consultation with the patients' physicians. Palliative prescribing included commencing 6 patients on morphine and 2 on benzodiazepines for dyspnoea, and 2 patients on diazepam for anxiety. Two patients underwent abdominal paracentesis for relief of uncomfortable ascites.

Seven patients required inpatient care only, 8 home care only, and 4 both. The median time of inpatient care was 15 days (range 1-63 days; all hospice admissions mean 15.6 days), and of home care was 25 days (range 1-867 days; all hospice patients mean 109.8 days).

Three patients were discharged before death. Of the remaining 16 patients, 10 died in the hospice and 6 at home.

This study shows that selected patients with heart failure can be managed by specialist palliative care which can address both inadequate symptom control and psychosocial and communication problems by drawing on its large experience in cancer. Patients with heart disease made similar demands on the specialist palliative care service when compared to other hospice patients. The majority of patients died in the hospice, a change in the place of death from standard care where a similar number died in hospital.<sup>3</sup> This study cannot determine whether specialist palliative care improved outcomes or indeed which interventions are appropriate in this group of patients. The role of specialist palliative care in providing services for patients with heart failure is yet to be determined.

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