Clopidogrel: a novel antiplatelet agent

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Clopidogrel is a novel antiplatelet agent that has a different mechanism of action to aspirin. Clopidogrel is chemically related to ticlopidine, both of which are more effective than aspirin in preventing some thrombotic events, but it has a safer side-effect profile than ticlopidine. It is likely to add to the antithrombotic armoury and reduce vascular mortality and morbidity more than current therapies.

Clopidogrel hydrogen sulphate is a platelet aggregation inhibitor. It is a thienopyridine derivative chemically related to ticlopidine (*Figure 1*), but it is reported to be six times more potent, and to have fewer side-effects (Feuerstein et al, 1995). It was launched in the UK in September 1998 by Sanofi Winthrop and Bristol-Myers Squibb as secondary prevention therapy in patients at high risk of ischaemic events as a result of a recent myocardial infarction or stroke, or established vascular disease.

Platelets have an established role in the pathophysiology of arterial thrombosis and ischaemic events in patients with atherosclerotic disease. It follows that agents that inhibit platelet aggregation should reduce the risk of thrombotic development. There is clear evidence from the Antiplatelet Trialists' Collaboration that aspirin and ticlopidine are of benefit in producing relative risk reductions in the composite outcomes of myocardial infarction, stroke and vascular death (Antiplatelet Trialists' Collaboration, 1994).

A large trial involving more than 3 000 patients showed that ticlopidine had a more pronounced effect on death from all causes or of non-fatal stroke than aspirin (Hass et al, 1989). Both aspirin and ticlopidine have potentially serious side-effects. With ticlopidine, its propensity to cause bone marrow suppression in particular has limited its usage in the UK.

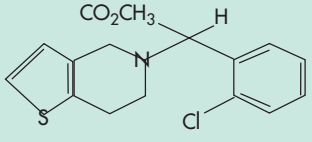

Figure 1. The chemical structure of clopidogrel.

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CLINICAL PHARMACOLOGY

Platelets may be activated by contact with a range of physiological substances including adenosine diphosphate (ADP). Platelet adhesion is dependent on the interactions of specific membrane receptors (glycoproteins), von Willebrand factor and fibrinogen. Clopidogrel selectively and irreversibly inhibits ADP-induced binding of fibrinogen to platelets by causing a major reduction in the ADP-induced activation of the membrane glycoprotein IIb/IIIa complex (Savi et al, 1996). Affected platelets are inhibited for their lifespan. Recovery of normal platelet function reflects the rate of platelet turnover.

DOSAGE AND ADMINISTRATION

A single daily oral dose of 75 mg is effective. Absorption exceeds 96% and is rapid with peak plasma levels of the main metabolite occurring approximately 1 hour after dosing. The elimination half-life is 8 hours.

CLINICAL TRIALS

CAPRIE was a randomized, double-blind, phase 3 clinical trial of clopidogrel (75 mg) *vs* aspirin (325 mg) in patients with atherosclerotic vascular disease manifested as recent ischaemic stroke, recent myocardial infarction or symptomatic peripheral artery disease (CAPRIE Steering Committee, 1996). Patients were followed up for 1–3 years. 19 185 patients with more than 6 300 in each group were recruited. The conclusions of the CAPRIE study were that long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction or vascular death (*Table 1*).

POTENTIAL CLINICAL USES

The rationale of the CAPRIE trial was that antiplatelet therapy is effective in reducing the risk of vascular ischaemic events in patients with atherosclerosis regardless of the initial manifestations of their disease. A new study presented at the American Congress of Cardiology in March 1999 (Clopidogrel Aspirin International Cooperative Study; CLASSICS) showed that clopidogrel with aspirin is better tolerated, and has similar efficacy, compared with ticlopidine and aspirin in coronary stenting. At present clopidogrel does not have a licence in the UK for use in coronary stenting.

TOXICOLOGY

Table 2 summarizes the reported adverse effects of aspirin and clopidogrel from the CAPRIE trial.

The overall safety profile of clopidogrel appears at least as good as that of medium dose aspirin. So far, only one case of aplastic anaemia in a patient receiving clopidogrel has been reported (Green, 1997), 17 months after starting clopidogrel. The patient was concomitantly receiving lovastatin, diltiazem and phenytoin, so the causal association is speculative.

CONCLUSIONS

Clopidogrel is an important alternative to aspirin in the prevention of ischaemic stroke, myocardial infarction and vascular death. Clopidogrel is as well tolerated as aspirin, but has fewer gastrointestinal side-effects, and appears more effective in preventing ischaemic events. Further clinical trials are needed to confirm these findings and the relative efficacy of clopidogrel compared to alternative doses of aspirin.

Although 325mg is an internationally accepted dose of aspirin in the prevention of thrombotic events, in some patients smaller doses may be indicated because of poor gastrointestinal tolerance. A dose of less than 325 mg of aspirin, e.g. 75 mg or 150 mg, may alter the relative safety profiles of aspirin and clopidogrel. Another area for possible trials in the future would be to study the effects of combining aspirin and clopidogrel therapy, as the two drugs have different modes of action. Although 30% of patients in CAPRIE were on lipid-lowering drugs without apparent problems, the role of concomitant lipid-lowering drugs needs to be properly evaluated as their use has steadily increased in secondary prevention of ischaemic events in patients with hyperlipidaemia. HM

TABLE 1.
Intention-to-treat analysis

Condition	Drug	Event rate per year %	Relative risk reduction (95% confidence interval)	*P* value
*Ischaemic stroke, vascular death, MI (primary endpoint)	Clopidogrel	5.32	8.7% (0.3–16.5)	0.043
	Aspirin	5.83		
Ischaemic stroke, MI, amputation or vascular death	Clopidogrel	5.56	7.6% (-0.8–15.3)	0.076
	Aspirin	6.01		
Vascular death	Clopidogrel	1.90	7.6% (-6.9–20.1)	0.290
	Aspirin	2.06		
Any stroke, MI or death from any cause	Clopidogrel	6043	7.0% (-0.9–14.2)	0.081
	Aspirin	6090		
Death from any cause	Clopidogrel	3.05	2.2% (-9.9–12.9)	0.710
	Aspirin	3.11		

*CAPRIE was not powered to demonstrate a statistically significant difference in secondary endpoints. MI = myocardial infarction. With permission of CAPRIE Steering Committee (1996)

TABLE 2.
Adverse events

	Aspirin	Clopidogrel
Rash	0.10%	0.26%
Diarrhoea	0.11%	0.23%
Upper GI discomfort	1022%	0.97%
Intracranial haemorrhage	0.47%	0.33%
GI haemorrhage	0.72%	0.52%
Neutrophils< 1.2×10^9/litre	0.17%	nil

GI = gastrointestinal. With permission from CAPRIE Steering Committee (1996)

Conflict of interest: None

Antiplatelet Trialists' Collaboration (1994) Collaborative overview of randomised trials of antiplatelet therapy I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *Br Med J* **308:** 81–106

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KEY POINTS

- Aspirin reduces vascular (non-fatal) events by 25% in a wide range of patients.
- Clopidogrel is a adenosine diphosphate receptor antagonist, and appears to have superior effects to aspirin in the prevention of myocardial infarction, stroke and vascular death.
- Clopidogrel's side-effect profile appears safer than ticlopidine, and comparable to aspirin, although it has fewer gastrointestinal side-effects than aspirin.
- Further studies to confirm the synergistic effect of clopidogrel and other antiplatelet drugs, and its use with lipid-lowering drugs are needed.