New Drugs

Antithrombotic treatment

P BUCKLER, A S DOUGLAS

Recent advances in the management of thrombotic disease have mainly been in prevention—for instance, prophylaxis of deep venous thrombosis. This article is confined to the use of drugs as possible prophylactic agents—namely, the antiplatelet drugs, low dose heparin, dextran, and anlod. All of these drugs are still being examined in different clinical settings, and the intention is to discuss the current state of evaluation of their clinical efficacy.

Antiplatelet drugs

The part that platelets play in initiation and propagation of thrombus remains controversial. Despite the theoretical benefits expected from the use of prophylactic antiplatelet treatment, the results of several large studies have so far shown only small unimportant trends in favour of treatment. There are many possible explanations why this should be, and with the expanding knowledge of platelet biochemistry it may be possible to develop more selectively potent drugs effective in small dosage. At the present time many drugs are known to modify platelet function (including the beta-blockers and calcium antagonists) but only three drugs are currently used specifically for their antiplatelet effects—namely, aspirin, sulphinpyrazone, and dipyridamole.

ASPIRIN

Platelet aggregation is a complex phenomenon and a vital part is played by prostaglandins, both in the platelet and in the vascular endothelial cells. The platelet contains enzymes that enable it to synthesise a prostaglandin called thromboxane, which is a potent stimulator of platelet aggregation. The endothelial cells, on the other hand, synthesise another prostaglandin called prostacyclin and this inhibits platelet aggregation. Both pathways use an enzyme called cyclo-oxygenase, although slightly different forms of this enzyme are found in the two types of cell. Aspirin irreversibly acetylates cyclo-oxygenase, and since the platelet is unable to resynthesise this enzyme, this effect of aspirin lasts for the lifespan of the platelet. Since thromboxane promotes platelet aggregation, it would be reasonable to expect that blocking thromboxane synthesis would have an antiaggregatory effect in vivo. Aspirin, however, also acetylates the endothelial cell cyclo-oxygenase, the result of which would be expected to enhance platelet aggregation. The endothelial cyclo-oxygenase can be regenerated in this nucleated cell; the cyclo-oxygenase in the platelet does not recover because this is a non-nucleated cell. It has been hoped that a dose of aspirin might be found that would totally acetylate the platelet cyclo-oxygenase but leave the enzyme largely unaltered in the endothelial cell. While work is still proceeding to establish such a dose there is now doubt whether a differential effect of aspirin can be established so that sufficient cyclo-oxygenase can be retained in the endothelial cell and none in the platelet. The daily dose of aspirin that may produce this differential is about 30-50 mg.

SULPHINPYRAZONE (ANTURAN)

Sulphinpyrazone was first developed as a possible substitute for phenylbutazone. While it has powerful uricosuric properties it lacks the analgesic and anti-inflammatory properties of phenylbutazone. Unlike phenylbutazone it has not been reported to cause severe blood dyscrasias. In 1967 Packham showed that both sulphinpyrazone and phenylbutazone could inhibit collagen induced platelet aggregation. The precise way in which sulphinpyrazone achieves this effect is not known, but it has been shown to act as a competitive inhibitor of prostaglandin synthesis in the platelet. Like aspirin it can also inhibit production of prostacyclin by the endothelial cells, although at the plasma concentrations achieved with therapeutic doses this is thought not to be of any importance.

DIPYRIDAMOLE (PERSANTIN)

Dipyridamole was introduced as a vasodilator and later found to have antiplatelet properties. At therapeutic doses, dipyridamole is a potent inhibitor of cyclic adenosine-5'-monophosphate (AMP) phosphodiesterase. The various prostaglandins (in particular prostacyclin) are believed to exert their effect on platelet aggregation through cyclic AMP. Prostacyclin increases the intraplatelet concentrations of cyclic AMP by stimulating the enzyme adenylate cyclase. By inhibiting the degradation of cyclic AMP, dipyridamole probably acts by potentiating the action of prostacyclin. At very high concentrations dipyridamole will also inhibit thromboxane synthetase, but this is thought unlikely to occur to any appreciable extent at the concentrations achieved with the doses used in man.

Dipyridamole is usually given together with aspirin because the two drugs are believed to be synergistic. Possibly the dose of aspirin in this combination is crucial, since too high a concentration of aspirin will inhibit prostacyclin synthesis and thereby negate the effect of dipyridamole. It could perhaps be argued that it would be better to combine sulphinpyrazone with...
dipyridamole, but to our knowledge no studies with this combination have as yet been undertaken.

**Antiplatelet drugs in clinical practice**

Several large studies have been and are being undertaken to assess the value of antiplatelet drugs as antithrombotic agents. Most of these studies have looked at arterial thrombotic disease, in particular the prevention of reinfarction after myocardial infarction and the prevention of stroke in patients with transient ischaemic attacks.

Two major causes of morbidity and mortality in the Western world are myocardial infarction and stroke. Antiplatelet treat-

ment might give some protection against these two conditions; the results from several large studies have so far shown only trends in favour of these drugs, and these trends have failed to reach statistical significance. In threatened stroke the Canadian Cooperative Study Group showed that aspirin conferred some protection to men with transient ischaemic attacks but not to women. Sulphinpyrazone gave no protection to either sex.

There have been six well designed and well conducted studies of aspirin treatment in survivors of myocardial infarction —involving 10 000 patients and 1000 deaths. Five of these studies showed trends in mortality in favour of aspirin; in the largest of all the studies (AMIS— aspirin myocardial infarction study) there was an excess of deaths in the group taking aspirin.

Two statisticians working separately have concluded that there is no inconsistency in the data and agree that the present evidence shows a 10 -15% reduction in total mortality by using aspirin. Unfortunately, we do not know what this dose should be; even small daily doses of 30 -50 mg of aspirin given for several days may block production of prostacyclin in the vessel wall. Aspirin with persantin has been examined in survivors of coronary thrombosis in the PARIS study (persantin (dipyridamole) aspirin reinfarction study). For total mortality during the first two years of the study, persantin plus aspirin gave better results than aspirin alone, which in turn was better than placebo; any differences, however, could have arisen by chance. For coronary incidence, however—that is, coronary death plus non-fatal myocardial reinfarction—those patients taking the combination of aspirin and dipyridamole did better than those taking the placebo. In the persantin (dipyridamole) aspirin reinfarction study the mortality benefit accrued in those patients who had entered the study within six months of the infarction. For this reason a second study using this combination of aspirin and dipyridamole is in progress to try to clarify these results.

The antorque reinfarction trial was thought at first to show that sulphinpyrazone prevented sudden death after myocardial infarction, but many criticisms have since been levelled at this study and the case for sulphinpyrazone at the moment is unproved.

Finally, the antiplatelet drugs have a role in preventing embolic problems in patients with prosthetic heart valves. Oral anticoagulant drugs have been shown to be better at preventing embolic phenomena than the antiplatelet drugs alone, but a few patients continue to suffer from embolic complications despite adequate anticoagulant control. In this group of patients the addition of dipyridamole to their anticoagulant regimen has probably conferred increased protection.

In summary, the indications for antiplatelet treatment are not clear cut. We recommend that aspirin (300 mg daily) is used in middle aged men with transient ischaemic attacks. The only other condition when we regularly use antiplatelet agents is in the initial management of patients with thrombocytopenia who have already had an embolic event. These patients usually start taking aspirin or dipyridamole at the same time as busulphan. To the best of our knowledge, however, no controlled study has yet been published to show that this combination of antiplatelet drugs and busulphan is of benefit.

All the antiplatelet drugs so far considered have side effects. Even at a dosage of 300 mg, aspirin can cause gastric irritation, although this may be negated to some extent by taking it either with or shortly after a meal. Dipyridamole has potent vaso-
dilator properties in addition to its antiplatelet action and this sometimes exacerbates angina pectoris. It should be used cautiously in patients with subvalvular aortic stenosis and also in those patients who have recently had a myocardial infarction with consequent haemodynamic instability. Dyspepsia, diarrhoea, and headache may also occur after starting treatment with dipyridamole but these are often dose related and dis-
appear if the dose is reduced. Although teratogenesis has not as yet been observed with dipyridamole, it should be used with caution in pregnancy. Sulphinpyrazone should also be used with caution in pregnancy and in patients with impaired renal function and nephrothiiasis. This drug can paradoxically precipitate acute attacks of gout. Dyspeptic symptoms may occur, but if a patient develops a rash or a blood dyscrasia while taking sulphinpyrazone then the drug should be stopped. Sulphinpyrazone also interacts with many other drugs—it potentiates the action of the coumarin anticoagulants as well as drugs that are bound to plasma proteins such as the oral hypo-
glycaemic agents.

As to doses the blood concentrations of these drugs may well be crucial for an optimum antiplatelet effect, this being par-
ticularly important with aspirin. We recommend that if one or more of these drugs is to be given as an antiplatelet drug then dipyridamole should be given 100 mg thrice daily before food, sulphinpyrazone 200 mg four times daily with food, and aspirin 300 mg once daily after food. These doses, however, are largely empirical, and future research may well indicate that different doses may be more beneficial.

**Low dose heparin**

The mechanism by which heparin influences the thrombotic process is complex since it affects many steps in the coagulation cascade, affects platelet adhesion and aggregation, reduces blood viscosity, and may induce the release of endogenous heparin like substances from cell surfaces.

Heparin may be administered in small doses in two ways. By common usage, low dose heparin is a term used for heparin being administered subcutaneously in a dose of 5000 units every eight hours or every 12 hours. At this concentration the major effect of heparin is believed to occur through its ability to accelerate the rate at which antithrombin III neutralises factor Xa and thrombin. Two formulations of heparin are currently available for subcutaneous use—namely, sodium heparin (heparin retard, minilip, uniparin) and calcium heparin (calciparine, minihep calcium), which is a mixture of the two salts. Subcutaneous calcium heparin gives lower plasma concentrations than sodium heparin and is believed to be equally efficacious in preventing thromboembolic disease. The lower plasma concentrations obtained with the calcium salt may reduce the risk of haemorrhagic complications.

The term ultra low dose heparin is reserved for heparin administered in very small doses via continuous intravenous infusion, usually at a dose of 1 U/kg/h. This method of ad-
ministration is reported to be effective as a prophylaxis against the development of deep venous thrombosis after operation and does not appear to increase the risk of haemorrhage. At the very low plasma concentrations obtained with ultra low dose heparin the heparin is unlikely to exert its prophylactic effects via antithrombin III. At these concentrations heparin is known to release lipoprotein lipase, which may in turn reduce the postoperative increase in platelet stickiness. At these low concentrations heparin induces the release of endogenous heparin like substances. This could well be important, since recent work with a semi synthetic analogue of heparin has shown it to be a poor anticoagulant in vitro, but in vivo it induces release of endogenous heparin like substances with anticoagulant properties comparable with those of heparin.
LOW DOSE HEPARIN IN PRACTICE

Many large studies have now shown that low dose subcutaneous heparin reduces the incidence of deep venous thrombosis in patients undergoing general surgery and those recovering from myocardial infarction and stroke. The results have not been so favourable in patients undergoing hip surgery, although combining subcutaneous heparin with oral dihydroergotamine gives increased protection to this group of patients. While providing protection against the development of deep venous thrombosis is desirable even more desirable is protecting against fatal pulmonary embolism. For a study to show such a benefit, large numbers of patients are required. One large study has claimed that subcutaneous heparin can reduce the incidence of fatal pulmonary embolism, but more large studies are needed to confirm this.

Subcutaneous heparin may be given as 5000 units every 8 hours or every 12 hours. The thrice daily regimen is probably more effective in preventing deep venous thrombosis in the high risk patient, although it carries a higher risk of haemorrhagic complications such as wound haematoma. For surgical patients the first dose should be given two hours before operation and then continued after operation until the patient is fully ambulant. For non-surgical patients the heparin should be started soon after admission and then continued until the patient is fully ambulant. In the clinical conditions mentioned no monitoring of treatment is required.

Ultra low dose heparin has only recently been tried but holds much promise. The heparin is given through a continuous intravenous infusion at a dose rate of 1 U/kg/h. The infusion is started at the time of operation and is then continued for the next two to five days, this interval depending on how long the patient receives intravenous fluids. Since this regimen has only recently been described more studies of its effectiveness are needed before it may be considered proved and suitable for routine use.

Dextran

In the early 1960s it became apparent that dextran (a volume expander) had an effect on clotting and shortly after this it was first used as a prophylactic measure against postoperative thromboembolism. Several studies have since shown that dextran (usually dextran 70) provides useful protection against the development of deep venous thrombosis and pulmonary embolism, although how this is achieved is not clear. Platelet adhesiveness and aggregation both decrease after an infusion of dextran, and this is probably due to interference with factor VIII. In addition, thrombi formed in the presence of dextran lyse more easily.

Both dextran 70 (Lomodex 70, Macrodex) and dextran 40 (Lomodex 40, Rheomacrodex) have antithrombotic actions, although Dextran 70 is the one most commonly used in clinical practice. Provided that there are no contraindications to its use, such as congestive cardiac failure, renal disease, or thrombocytopenia, the dextran may either be infused as one dose (usually 1000 ml) at the time of operation or alternatively 500 ml may be infused at the time of operation and then a further 500 ml infused the next day. Both regimens are effective, and choice depends on individual preferences.

Ancrod

Ancrod is the venom obtained from the Malayan pit viper (Agkistrodon Rhodostoma) and it acts by converting fibrinogen to an unstable form of fibrin that is then rapidly removed from the circulation. Ancrod given after operation provides effective prophylaxis against deep venous thrombosis developing in patients undergoing surgery for fractured neck of femur. It is suggested that the patient be given 280 units subcutaneously immediately after the operation and then a further 70 units subcutaneously each day for the next four days. This regimen has not been reported to carry an increased risk of haemorrhagic complications.

Ancrod is contraindicated in the following conditions: pregnancy, septicaemia, gastrointestinal pathology if the lesion might bleed, and, finally, if a bleeding diathesis is present. It is also contraindicated if a plasma expander (such as dextran) has been used. Should a patient become haemorrhagic an antidote is available, but the reader is recommended to follow the manufacturer’s instructions carefully. If life threatening haemorrhage should occur the patient should be given fibrinogen or if this is unavailable fresh plasma or whole blood.

While undoubtedly effective in preventing the development of deep venous thrombosis ancrod is expensive, and what is now required is a larger study to determine whether it is effective at reducing the postoperative morbidity rate from pulmonary embolism.

Bibliography


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An overview of the clinical and pathological effects of ancrod and ancrod, as described by the author in this and other topics, discusses how heparin and dextran are believed to exert their antithrombotic effects.


A review discussing how low dose heparin and ultra low dose heparin are believed to exert their antithrombotic effects.


A concise review on the use of ancrod in thrombotic disease.


A review of studies to date including the re-evaluation of the Anturane reinfarction trial (p 1005, same issue).

Why do some elderly patients with hypertension whose blood pressure returns to normal on treatment remain normotensive when treatment is stopped? Is there such a phenomenon as “burnt out” hypertension?

There is a tendency in some subjects for an observed raised blood pressure to fall to normal levels on repeated examination. Pickering, in younger people, considered the raised pressure to be a defence reflex followed by its gradual extinction with repeated visits and blood pressure measurements. Colandrea et al, in a study of 3246 subjects in a retirement community (average age almost 70), noted the prevalence of systolic hypertension (defined as systolic more than 160 mm and diastolic less than 90 mm) to fall from 14% on initial screening to 2.7%, on the third visit to the clinic. Adams, also in the elderly, noted the frequent tendency for the blood pressure to fall spontaneously after a stroke. There seem, therefore, to be groups of people at all ages whose apparently raised blood pressure fails to normalise on repeated examination, some perhaps for “psychophysiological” reasons, others after pathological events. The influence of treatment given in such instances may be entirely coincidental, underlying the necessity to establish the true level of the blood pressure in the elderly by repeated measurements over a period before embarking on treatment. “Burnt out” hypertension as a phenomenon should be viewed with suspicion. Except under the conditions outlined above, a drop in blood pressure is much more likely to be an indicator of unsuspected pathology—for example, a silent myocardial infarction, pulmonary embolism, concealed blood loss from the gastrointestinal tract, etc.—B MOORE-SMITH, consultant in geriatrics, Ipswich.