in patients treated for the shorter period (18·1% versus 9·5%). The excess tended to occur soon after treatment was stopped. Furthermore, the overall rate of recurrence was much lower (6.6%) in patients with temporary risk factors (surgery, trauma, temporary immobilisation, travel, oestrogen treatment, infection, Baker's cyst, and pregnancy) than in those with permanent risk factors (defined as venous insufficiency, idiopathic venous thromboembolism, and systemic lupus erythematosus—18%). It should be noted that in neither study was there a difference in mortality, fatal pulmonary embolism, or the incidence of major bleeding between the longer and shorter durations of treatment.

On the basis of the above studies, it is becoming feasible to identify patients at greater risk of recurrence after oral anticoagulant treatment is stopped. Not surprisingly, these comprise patients with continuous risk factors, such as malignancy, "idiopathic" venous thromboembolism, inherited disorders of coagulation inhibitors (antithrombin III, protein C, and protein S deficiencies), and lupus-type antibodies. The recently identified and more common factor V Leiden mutation[8] will probably also fall into this category. In neither of the trials of oral anticoagulants that examined duration of treatment, however, were these latter groups analysed. Indeed, in the second study patients with congenital defects were specifically excluded.[6] Patients with permanent risk factors should be given anticoagulants for at least six months after an unprovoked episode of venous thromboembolism, and in some (for example, those with malignant disease, lupus-type antibodies,[9] or inherited disorders of coagulation inhibitors) longer term or indefinite treatment should be considered. Uncertainty persists in these categories.

Patients with reversible risk factors for venous thromboembolism, such as surgery, trauma, or temporary immobilisation, do not require long term oral anticoagulants, and on the available evidence these drugs may be reasonably suspended after four to six weeks.

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To β block or better block?

β_1 *selectivity rarely matters in clinical practice despite the hype*

Scarcely a week now passes without a new receptor subtype being described on which either endogenous neurotransmitters or hormones might act, usually as agonists, and which are rapidly proposed as novel targets for drugs, usually as antagonists. It is therefore ironic, but instructive, to recognise the debate that still stirs among doctors and pharmacologists over the relative merits of β_1 selective and non-selective β blockade after more than 20 years' use in angina and hypertension.

The most recent airing of the debate concerned the paradoxical pressor response to non-selective β blockade.[1,2] In the absence of β blockade, acute rises in circulating adrenaline concentrations hardly affect mean blood pressure because of opposing actions on systolic and diastolic blood pressure. The rise in systolic blood pressure is due mainly to vasoconstriction mediated by α adrenoceptors, and this is unopposed when a non-selective β blocker like propranolol prevents the vasodilatation mediated by β_2 adrenoreceptors. But two obstacles exist to concluding that selective β_1 blockade must automatically be preferable.

Firstly, it is necessary to appreciate that the endocrine secretion of adrenaline from the adrenal medulla rarely achieves the circulating concentrations necessary to contribute substantially to the control of blood pressure, with the main catecholamine being noradrenaline released from sympathetic nerve endings.[3] Noradrenaline has about the same 20-fold selectivity for β_1 receptors (compared with β_2 receptors) as an agonist as does atenolol as an antagonist, meaning that under most circumstances selective β_1 blockade is protecting against a non-existent "enemy" of peripheral blockade of β_2 receptors.[4]

Under what circumstances may release of adrenaline be exceptional? The three instances most relevant to patients likely to be receiving β blockers are hypoglycaemia, myocardial infarction, and phaeochromocytoma.[5-7] The first of these is the only instance in which adrenaline's activation of β_2 adrenoreceptors is positively beneficial, by contributing to the patient's warning symptoms and by accelerating metabolic recovery from hypoglycaemia; insulin dependent diabetic patients are therefore the only ones for whom selective β_1 blockade is unequivocally an advantage.

In the remaining groups of patients the argument against non-selective blockade has rested on the paradoxical pressor response. This, however, is readily prevented by α blockade in patients with phaeochromocytoma, who in any case need only low doses of β blockers to protect against cardiac effects of their circulating catecholamines. In myocardial infarction the questions to be answered are whether a small paradoxical pressor response is necessarily harmful and whether there are benefits from blocking both β receptor subtypes. This latter question arises because of the realisation during the past decade that the human heart has a substantial population of functional β_2 receptors, which may contribute as much as β_1 receptors to the arrhythmias that kill about 30% of patients before they reach hospital.[8,9] In addition, hypokalaemia mediated by adrenaline, through activation of β_2 receptors, may enhance the risk of arrhythmia.[10,11] Selective β_1 blockade —for instance by atenolol—not only leaves β_2 receptors unprotected but causes a paradoxical fivefold to tenfold increase in their sensitivity to adrenaline, through an enhanced coupling to G protein activation of adenyl cyclase.[12-14]

It is intriguing that in the various secondary prevention

trials of β blockade after myocardial infarction the benefit conferred by β blockers was slightly better in those that used non-selective agents such as timolol and propranolol. A regionwide study in East Anglia is now directly comparing non-selective and β_1 selective blockade in secondary prevention. Meanwhile, an interesting testimony to the influences over prescribing habits is the fact that the most widely used β blocker in secondary prevention is atenolol, which has never itself been tested in a secondary prevention trial. Atenolol has survived questions about its disappointing efficacy in several other trials of outcome, perhaps related to its uniqueness as a water soluble β blocker. The first international trial of infarct survival studied short term use of atenolol in myocardial infarction, and it is again intriguing that the drug prevented cardiac rupture but not arrhythmias.

It is now becoming apparent that these large trials fail to shed light on interesting pharmacogenetic differences that may be more important to individual patients than small albeit significant differences between groups in trials. The β_2 adrenoreceptor is one of several candidate genes for essential hypertension, in which both genetic polymorphism and a possible association with hypertension have been reported. The search for the genetic basis of hypertension and ischaemic heart disease might be helped by clinical identification of families in which paradoxical responses to non-selective β blockade are extreme. Until current trials tell us otherwise, therefore, doctors can be encouraged to use either type of β blocker and can expect to note individual differences in the short term changes in symptoms or blood pressure.

Above all, doctors should remember the injunction to first do no harm, and arguments about which β blocker to use pale into insignificance before the absolute indictment against any β blocker, even locally as eye drops, in patients with a history of asthma. Few clinicians may understand the niceties of receptor selectivity. Fewer still understand that the high potency of a drug required to permit its local administration is synonymous with a high receptor affinity and very slow dissociation of drug from receptor. One drop of timolol down the lacrimal duct can kill.

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Magnesium sulphate: the drug of choice in eclampsia

Definitive trial signals triumph for researchers in the developing world

Until this year, the pharmacological treatment of eclampsia has been determined largely by geography, habit, and prejudice. Magnesium sulphate has been the drug of choice in the United States; in Britain, diazepam and, more recently, phenytoin have been favoured.[1] None of these choices was influenced by strong scientific evidence.

A network of researchers has recently reported the first large randomised trial comparing these three drugs in eclampsia.[2] The collaborative eclampsia trial is the most important obstetric trial of the 20th century, and it has set new standards for vision and ambition in clinical trials in perinatal medicine. It included no fewer than 1680 eclamptic women recruited by local clinicians in west and southern Africa, South America, and India; and the trial was coordinated mainly by the National Perinatal Epidemiology Unit in Oxford. Data were obtained from more than 99·5% of the women recruited.

The trial has produced compelling support for the use of magnesium sulphate. Women were 52% and 67% less likely to suffer recurrent fits after treatment with magnesium sulphate than with, respectively, diazepam or phenytoin. They were 26% and 50% less likely to die after magnesium sulphate than with, respectively, diazepam or phenytoin (although these changes in death rates were not significant). No clear evidence emerged that treating mothers with magnesium sulphate was either advantageous or disadvantageous to the fetuses, at least in the short term.

Traditional British arguments against the use of magnesium sulphate centre on its perceived toxicity and the difficulties in measuring magnesium concentrations during treatment. The issue of toxicity has been dispelled, at least in comparison with that of diazepam and phenytoin, and magnesium concentrations were not measured routinely (many centres would have found this impossible even if it were possible to determine the therapeutic range).

Complementary information on the value of magnesium sulphate now comes from the United States.[3] In a trial of anticonvulsant prophylaxis in 2138 women with hypertension during labour 10 of 1089 treated with phenytoin went on to have eclamptic fits while none of the 1049 women treated with magnesium sulphate did.

If the case for using magnesium sulphate in eclampsia is now clear then the place of anticonvulsant prophylaxis in pre-eclampsia is less certain. If an anticonvulsant is to be given to pre-eclamptic women then magnesium sulphate is now the agent of choice. An estimated 5% of pregnant women in the United States, however, receive anticonvulsant treatment,[3] which surely represents gross overtreatment; only 0·5% of treated hypertensive women in the Texas trial actually had convulsions.