Oral anticoagulants reassessed

Treatment with oral anticoagulants fell into disrepute in the 1960s partly as a result of the poor results of controlled trials in patients with cardiac infarction and partly because of the high frequency of haemorrhagic side effects. Gradually, however, this disenchantment with anticoagulants has been dispelled as newer methods of assessment and monitoring have been introduced. The combination of the British system for anticoagulant control and the United Kingdom external quality assessment scheme in blood coagulation testing has placed anticoagulant treatment on a safer foundation.[1] The system is based on a recommended technique using the standardised reference thromboplastin, British comparative thromboplastin,[2] provided by the National Reference Laboratory for Anticoagulant Reagents and Control at Manchester. Results are reported as the patient's prothrombin time compared with the British comparative thromboplastin normal value—that is, the British ratio. External quality control exercises were started in the early 1970s to check the effectiveness of the British system, and these developed into the external quality assessment scheme in blood coagulation. Since then the range of tests has been broadened, and all the main hospital centres are now included. These exercises have resulted in a substantial improvement in laboratory performance.[3]

Manchester comparative reagent, which is equivalent to British comparative thromboplastin, is now used routinely in over 95% of British hospitals. The remainder are asked to interpret their results with local home-made or commercial thromboplastin in terms of the British comparative thromboplastin to conform to the British ratio scale of reporting. Most British hospitals now use a British ratio range of 2·0 to 4·0 when monitoring their patients' treatment.[4]

Added importance has been given to these aspects of laboratory control by new randomised studies which have provided reliable evidence of the value of oral anticoagulants in the short-term prophylaxis and treatment of deep vein thrombosis[5 6] and even in the long-term management of myocardial infarction.[7] Furthermore, the last decade has seen a dramatic increase in the extent of the use of coumarin drugs in British hospitals as a result of the increased recognition of the true incidence of deep vein thrombosis by the introduction of new non-invasive techniques of diagnosis and of reappraisal of the role of coumarin drugs in other clinical states.

Why, then, had anticoagulants fallen out of favour? The poor results of clinical trials in myocardial infarction[8 9] were almost certainly due to the treatment having failed to provide adequate anticoagulant protection. New laboratory techniques for regulating coumarin dosage had been introduced which masked the inadequacy of the amounts of drugs prescribed. As Mitchell[10] recently stated, it was as though a new method for blood glucose estimation had been introduced which suddenly gave lower readings.

A second reason for clinicians' reluctance to use anticoagulants had been their fears of haemorrhagic complications. Bleeding was much more common in many other countries than in Britain; the fault lay in the use of different tests of prothrombin time, incorporating animal tissue thromboplastins. Such techniques are relatively insensitive to reductions of extrinsic clotting factors II, VII, and X resulting from administration of coumarins and thus do not adequately gauge the depression of coagulability. One recent comparative study[11] has shown that an apparent conservative twofold prolongation of the prothrombin time with Simplastin, one of the most widely used United States reagents, was equivalent to results far beyond the limit of safety (up to an eightfold prolongation) when the patients' samples were tested in parallel with British comparative thromboplastin. In another report all of a group of patients having treatment long term and British ratios between 2·0 and 4·0 would have been regarded as undertreated according to the results of tests with Simplastin.[12]

The effectiveness of the therapeutic range with British comparative thromboplastin has been adequately validated by many years of clinical study in British hospitals and by clinical trials. There is good reason to believe, therefore, that the higher incidence of haemorrhage still noted in studies from the North American continent[6 13] could be reduced by using a more conservative regimen. Studies are in progress to attempt to settle this question.

In an article published earlier this year Duxbury[1] proposed a form of medical audit—that is, therapeutic quality control—for patients having anticoagulants. He devised a simple scheme for assessing the success of dosage with British comparative thromboplastin and assessed his own results. In short-term treatment only about half of his patients proved to be taking an adequate dose. The results in patients managed for up to one year were considerably better, roughly 70% being adequately dosed. Anticoagulant treatment is expensive, and Duxbury suggests that some scheme is needed for medical assessment of the cost effectiveness of anticoagulant treatment.

Usually published trials give no data on the effectiveness of anticoagulant treatment. The recent Netherlands 60-plus reinfarction study of myocardial infarction was a welcome exception. Over 70% of test results were within the therapeutic range of 5 to 10% Thrombotest, equivalent to British ratios of 2·7 to 4·5. The total mortality was significantly higher in the placebo group (13·4%) than in the treated group (7·6%) over a two-year period. The incidence of major bleeding complications was gratifyingly low,[14] being about one in 25 years of treatment, which compares closely to the results with the British system for anticoagulant control reported by Forfar.[15]

Comparable success would not necessarily be achieved everywhere if there were an uncritical wholesale return to anticoagulant administration for myocardial infarction. The dangers would still probably outweigh the benefits unless good facilities were available for anticoagulant control with the use of an effective and safe therapeutic regimen allied to skilful clinical dosage incorporating some degree of therapeutic quality control. With the British system for anticoagulant control supported by the United Kingdom external quality assessment scheme in blood coagulation, our hospitals are now in a privileged position to assess the clinical effectiveness of anticoagulants in myocardial infarction and in a whole range of clinical settings where benefit from oral anticoagulant administration is still controversial or remains to be established on a firm statistical basis.

LEON POLLER

Director,
National (UK) Reference Laboratory for
Anticoagulant Reagents and Control,
Withington Hospital,
Manchester M20 8LR

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Rejecting scientific advice

The decision[1] by Mr Kenneth Clarke, Minister of Health, to refuse approval for the long-term use of the contraceptive medroxyprogesterone acetate (Depo-Provera) is yet another example of Government rejection of the considered judgment of its scientific advisory bodies.

Clearly the Committee on Safety of Medicines had looked at the issue very carefully. The drug has been the target of sustained attack by the Campaign Against Depo-Provera, which claims that it is given to socially deprived, black or Asian women without their being fully informed of its possible side effects and dangers.[1] Nevertheless, medroxyprogesterone acetate has been used for 20 years in many countries, and a recent television programme (BBC2, 1 March) reported that doctors in Thailand found the drug valuable and were surprised at the "unbelievable overstatements" of the pressure groups.[2]

Here in Britain the Family Planning Association lists medroxyprogesterone acetate as the last of its eight choices for couples wanting contraception, and the Committee on Safety of Medicines recommended that the drug should be used only when all other sorts of contraception have proved unsatisfactory. This guarded acceptance for medroxyprogesterone acetate is due to question marks over its safety and its clinical drawbacks. Firstly, tumours have been reported in monkeys given 50 times the normal dose; the Committee on Safety of Medicines comments that the "relevance of this to man has not been established." Some women given the drug have developed breast cancer—but the association is unlikely to be causal. Secondly, the drug causes unacceptable side effects in many women—menstrual bleeding becomes irregular and unpredictable and may be heavy and prolonged.

Yet with all the evidence before it the Committee on Safety of Medicines was prepared to approve the drug. Mr Clarke would not accept that advice.[1] The Government believed that the possible risks outweighed the benefits, he said, adding that "Each individual doctor cannot make a judgment about whether a particular drug is necessarily safe. They rely on the licensing system."

As we have argued before,[3] the Government should not reject the advice of its own experts without giving its specific detailed reasons for doing so. On this occasion Mr Clarke seems to have been swayed by anecdotal reports of the drug being given to mentally handicapped or mentally ill women without their informed consent. What he is saying in effect, however, is that doctors cannot be trusted to exercise competent clinical judgment in the use of a second-line drug.

Certainly there is room for improvement in the standards of prescribing in the NHS, and by no means all official warnings about drugs are heeded by prescribers. But the Committee on Safety of Medicines was set up to assess the safety of drugs on objective grounds; it has a high reputation around the world for balancing the needs of consumers against the needs of doctors and the pharmaceutical industry. Doctors have learned to pay close attention to its advice, and this is especially true of its advice on contraceptives.

In these circumstances Mr Clarke may reasonably be asked to give a much more detailed and convincing justification for his decision. Without such an explanation his actions are unacceptably authoritarian.

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Blood group antigens and bladder cancer

The discovery of A and B blood group antigens on the surface of human epithelial cells[1] and of their absence from carcinomatous tissues[2] led to the hope that this difference might give an early objective indication of neoplastic dedifferentiation. Using exfoliated cells from bladder tumours Kay and Wallace[3] showed loss of blood antigens from patients with invasive and metastatic disease. Nevertheless, the correlation between detectability of A and B antigens and the clinical course was not close enough to be clinically useful.

Recently there has been a considerable resurgence of interest in a modification of the original test, using paraffin embedded sections and a sandwich technique with grouping sera and indicator erythrocytes of the appropriate blood group. Thus retrospective studies are possible, and indeed over a dozen papers have been published, mainly in American journals, in the last three years.[4–15] For most sceptical watchers of tests for cancer the conclusions seem too good to be true.

The consensus gives grounds for great optimism, particularly in the early recognition of the one patient in five with a superficial tumour of the bladder who will ultimately develop an invasive recurrence. To summarise, patients with superficial cancer whose cells have the appropriate surface blood group antigen have a good prognosis with only a 5% chance of developing invasive recurrence. The test may be a better index of subsequent aggressive tumour behaviour than cell grading. A recent critical review[16] showed that of 100 patients with high grade tumours 23 had a positive test for antigen, and only one of these went on to become invasive. The author emphasised that the test could be of most use in this group, since such patients might escape cystectomy at the hands of a surgeon who

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