ALTERNATIVE THROMBOTIC THERAPY

P. Turkington

Institute of Health Care,
University of Malta

Thrombotic disease is very much a Twentieth Century killer. Epidemiological studies have established its effect both in terms of decreasing the quality of life and in the ever increasing number of fatalities. Numerous risk factors and risk groups have been identified not least of which is increasing age. This is frequently reflected in the number of elderly patients attending anticoagulant clinics of which Malta is no exception. Traditional therapy has by in large concentrated on the use of warfarin as a first line drug in preventing recurrent thrombotic episodes. The action of warfarin is however not specifically directed against the active site of coagulation proteinases but rather inhibits a post ribosomal carboxylation of vitamin K dependent clotting factors which leads to a decrease in the amount of thrombin the body can generate per unit time.

More recently attempts have been made to inactivate the active site of coagulation proteinases rather than reduce the concentration of their inactive zymogens. This has lead workers to utilise high molecular mass inhibitors such as eglin c and hirudin or low molecular mass inhibitors such as peptidyl alpha-aminoalkylphosphonate diphenyl esters and 7-acylamino derivatives of isocoumarins. The use of low molecular mass inhibitors looks promising and can be designed to inactivate specific serine proteinases. Problems of solubility, stability and cross reactivity do exist but can be overcome by modifications which maintain their effectiveness without a loss in potency. At present we are examining the effectiveness of peptidyl alpha-aminoalkylphosphonate diphenyl esters in inactivating serine

proteinases. The results show a kobs/[I] = 15,000 M - 1s - 1 towards cathepin G and 0.1 M - 1s - 1 for thrombin. Modifications to the peptide are currently being made in Queen's University, Belfast and will be further examined for their solubility and inhibitory capacity. This line of research may yield a more effective mechanism by which we control systemically generated serine proteinases and thereby the disease process.