Radiographic, Haemodynamic and Biochemical Findings Related to the National Heart and Lung Institute's Urokinase Pulmonary Embolism Trial

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Eighty-two randomized patients with pulmonary embolism of five days' or less duration were treated with urokinase (UK), 2 000 CTA units/lb body weight followed by 2 000 CTA units/lb/hr for 12 hours. Results were compared with 78 control patients treated with 75 units of heparin/lb followed by continuous infusion of 10 units/lb/hr for the same period. All patients were then placed on heparin and, subsequently, on anticoagulants, 24 hours after the initiation of therapy. Resolution was significantly greater in the UK group as shown by repeat pulmonary angiography (critical ratio¹ of 7.8 and RBO² of 2.9×10^{-13}). Lung scan changes were also significant but of less magnitude (critical ratio of 3.3 and RBO of 5×10^{-2}). The differences between the urokinase- and heparin-treated groups diminished progressively until day seven of therapy when scan resolutions were the same. Significant differences were also observed in right-sided haemodynamics and in total pulmonary resistance, but not for changes in cardiac output or A-V O₂ extraction. Pulmonary angiography and right-sided pressures showed greater differences in patients with massive emboli than in those with submassive emboli. The treatment effect, by lung scan, was significant for pulmonary emboli less than 48 hours old but not for older emboli.

Biochemical data on plasma samples from urokinase-treated patients also showed highly significant changes: the mean pre- and postinfusion plasma levels for plasminogen decreased from 2.12 to 0.60 CTA units/ml, and for fibrinogen from 515 to 268 mg/100 ml while the mean of the whole blood euglobulin lysis times changed from 200 min before infusion to 16 min after infusion. Samples from heparin in treated controls showed little or no change. Assays for circulating urokinase revealed about 50 CTA units/ml during the infusion period.

In view of these highly significant clinical and biochemical data, the correlation coefficients were calculated for angiographic changes (toward normal) after infusion of urokinase vs. the biochemical (fibrinolytic) changes in the patient's plasma or the

haemodynamic changes over the same time period. Correlation coefficients for the various parameters were: scan 0.32, pulmonary artery pressure 0.19, right atrial pressure 0.27, fibrinogen 0.03, plasminogen 0.02, and change in whole blood euglobulin lysis time 0.00. The extraordinary lack of correlation between embolus resolution and degree of activation of the fibrinolytic system led us to conclude that at this dosage of urokinase the patients' clinical response probably depends primarily upon local factors in the area of embolization (such as age of embolus), and also patients can develop a clinically useful thrombolytic system whether they show marked biochemical changes in response to urokinase therapy or not.

In addition, analysis of the data before infusion indicated decreased levels of plasminogen, fibrinogen, and platelets and increased prothrombin times in 38 (of 140) patients suggesting possible defibrination. Seven (19%) of the 38 patients in this group died as compared with three (3%) of 102 with more normal laboratory findings before infusion. The incidence of severe haemorrhage was also higher in this group (38%) than in the others (16.5%)

Drug Therapeutic Evaluation in Acute Myocardial Infarction

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For the last two decades, the statistically controlled therapeutic trial in acute myocardial infarction has involved, largely as a result of British advocacy, only the very simplest of design concepts. Essentially, it has been held that provided all necessary precautions were taken strictly to randomize patients into a study and other precautions taken to avoid bias in patient selection, that the determination of relative mortality between treated and control patient groups would suffice to determine a single drug's therapeutic efficacy and therapeutic value.

Such trial design principles appeal mainly to administrators and statisticians. To the former, since they are simple to understand and relatively easy, though tedious, to organize on a practical basis. To the statisticians, because they feel that in dealing with mortality, they are dealing with 'hard' data and thus, difficulties in statistical analysis of results will be minimized.

However, the experience of the last 25 years, especially with trials of anticoagulant therapy, have shown trials of the conventional type to display many weaknesses. (1) They are extremely inefficient insofar as they utilize only a very small fraction of the data collected. Since only the actual death of a

¹Critical ratio = $\frac{\text{treatment difference}}{\text{standard error}}$ 2.5 = borderline, 3.0 = fully significant.

²RBO = relative betting odds.

patient constitutes a statistically significant event, and since patient mortality in this disease is now under 20% in the best coronary units, over 80% of the collected data is essentially discarded in the final analysis. (2) The logical basis for using patient death as a primary trial endpoint can be challenged on several grounds and, (3) finally, our present types of clinical trial are of such extraordinary inflexibility and also necessitate the study of such large patient groups that there are crippling limitations concerning the number of relevant trial factors that can be examined in any single trial. Thus, the conclusion of any one trial immediately results in the necessity to run further trials in order to clarify points that have been raised.

Especially since the future will bring more drugs whose therapeutic efficacy in the patient with acute myocardial infarction will require assessment, and also because we are already in the position with drugs such as urokinase, where we will have to run individual trials with different dosage schedules, the urgency to improve therapeutic trial designs in acute myocardial infarction is obvious.

Whereas there can be no doubt as to the importance of undertaking further control clinical trials of thrombolytic therapy in acute myocardial infarction, there must be considerable uncertainty as to the most appropriate form of clinical trial.

There are three main possibilities: (1) to undertake a conventional control clinical trial using appro-

priate randomization and taking relative patient mortality as the sole criterion of treatment success—the design used in virtually all anticoagulant trials in acute myocardial infarction over the past two decades and a design that has proved less than adequate in practice; (2) to attempt to improve trial design sensitivity, acknowledged to be low, while retaining relative patient mortality as the main criterion of treatment success; and (3) to attempt to devise clinical trial designs in which criteria of drug action, other than relative patient mortality, are of predominant importance.

Advances in our understanding of the natural history of acute myocardial infarction, in cardiological practice, and particularly in the development of biomedical computer instrumentation, make the last possibility both feasible and attractive. Such a decision is also attractive from a more fundamental standpoint, for many of our difficulties in this field arise from the fact that while we as investigators are really interested, especially in a complex disease such as myocardial infarction, in the evaluation of multiple treatment effects, current statistical theory is geared to the concept of assessing the significance of a single variable. Consequently, if methods can be developed, and there is good evidence they can be, to measure multiple responses in the surviving patient, clinical trial concepts in acute myocardial infarction would then become adequate to the heavy task before us.