Heberden Society

Clinical Meeting, Stoke-on-Trent, June, 1973

At a clinical meeting held at the North Staffordshire Medical Institute, Hartshill, Stoke-on-Trent, on June 1, 1973, the following papers were given.

Technique for Assessing the Potential Effectiveness of Antirheumatic Drugs. By P. LEE, J. WEBB, J. ANDERSON, and W. W. BUCHANAN (*Glasgow*)

Many of the clinical and laboratory indices usually included in current trials of anti-rheumatic drugs may not be relevant to the assessment of the potential therapeutic value of the drug. It can be argued that the only relevant feature of an anti-rheumatic drug is its ability to relieve pain.

A 14-day single-blind trial of prednisone, aspirin, and placebo was carried out in 128 patients suffering from rheumatoid arthritis, using subjective parameters only. Patients were instructed to record daily their severity of pain on a pain chart incorporating a 5-point nominal scale representing the five degrees of pain: 'none', 'mild', 'moderate', 'severe', and 'very severe'. At the end of the trial patients were asked to rate the drug according to the five general scores of satisfaction: 'totally ineffective', 'ineffective', 'moderately effective', 'effective', and 'highly effective'. For statistical analysis a scale of 1 to 5 was allocated to both the pain scale and patients' general satisfaction.

The pain scores for the duration of the trial were averaged in each case and an average 'treated pain rating' was established for each drug (placebo 3.47; aspirin 3.0; prednisone 2.56). The differences between each drug are all highly significant ($P < 0.001$). Various pre-treatment observations, including severity and duration of disease, were tested by analysis of covariance, and only the initial pain score and articular index of joint tenderness were found to be significantly related to the average treated pain rating. When the mean patient satisfaction rating was calculated for each drug (placebo 1.70; aspirin 2.36; prednisone 3.68) the differences of the means were highly significant ($P < 0.001$). The calculated mean numbers of days withdrawn on each drug were also significantly different, implying that the more effective the therapy the less the chance of the patient's withdrawing from the trial.

The method described appears to be useful in the assessment of the effectiveness of anti-rheumatic drugs and may be sufficiently sensitive for the comparison not only of different drugs but also different doses of the same drug.

Discussion

DR. R. M. MASON (*London*) Were the patients told that they were to be given corticosteroids?

DR. LEE These patients were not told that they were being given corticosteroids. They were randomly allocated to one of the three drugs.

DR. R. M. MASON (*London*) Was their consent obtained?

DR. LEE Yes.

PROF. V. WRIGHT (*Leeds*) I think the ethical problem lies not in whether the patient had prednisone but rather in whether it is ethical to give rheumatoid patients a placebo. Whilst I think your ultimate conclusion is very good, one has a little reservation about seeing slides that discuss 'mean pain', for instance. I think it is important to appreciate that these are non-orthogonal data. This is a case where four times one does not equal four, and when you see 'mean' you might think it did.

DR. LEE I agree with your comments about the scoring system. We discussed the problem at length and this will be published. It is recognized that there is not a linear relationship between the different scores, but we could not find a better method of scoring. One could weight the scoring system, but we decided to keep the method simple.

DR. P. H. N. WOOD (*Manchester*) The attempt to simplify clinical trials is welcome, as is the attachment of greater weight to the patient's opinion. But I am not clear why you reject a cross-over design; I suspect that a single drug administration without cross-over is false economy. Means can be very misleading when comparing two groups of people who are not necessarily similar. Moreover, I do not find your evidence satisfactory enough to convince me that your method is necessarily reproducible, just because you have done another trial and have happened to get similar mean pain scores.

DR. LEE I agree that different patients can respond very differently to one medication but this is a single-blind trial in which we hoped to overcome some of these problems by using large numbers, at least fifty patients in each trial. In the pilot trial we ended with about forty-two to forty-five patients in each category. As regards the reproducibility of the method for pain rating, the mean initial pain ratings of the patients on aspirin in the two groups are fairly similar with 2.88 and 2.77 respectively.

These I have not analysed and therefore cannot tell you whether they are significantly different, but the second trial suggests that it is reproducible.

DR. P. H. N. WOOD (*Manchester*) I am very dubious of the power of statistics to answer that particular problem. Reproducibility, for instance, is a function of one patient; you can establish reproducibility only by the fact that it is individually reproducible in individual patients and I do not think your method is revealing this at the moment.

DR. A. ST. J. DIXON (*Bath*) The paper has put forward a claim that this is a simple method, using the out-patient material we have, for screening drugs without too much elaboration, and I think, Dr. Wood, that neither you, nor the authors, have claimed that the statistics are at fault here, or that this could be substituted for a full-dress double-blind trial.

DR. LEE I agree, we do not cite this as the be-all and end-all of all clinical trials. I stated in the discussion that this may be a useful adjunct in the trial of the therapeutic effectiveness of anti-rheumatic drugs; it is not designed to replace the present standard methods.

DR. I. HASLOCK (*Leeds*) It has been suggested that relief of symptoms in rheumatoid arthritis is related not only to analgesia but also to anti-inflammatory activity. As your assessment appears to rely heavily on pain relief; when you used paracetamol, which has no anti-inflammatory action, in your second trial, did you in fact find that this was different from the anti-inflammatory agents?

DR. LEE We did not. Looking at the raw data, the results with paracetamol are not very impressive; the figures are not much higher than those we obtained with the placebo.

DNA-binding in Rheumatoid Arthritis. By P. G. ROCHMIS, H. PALEFSKY, H. ROTH, M. BECKER, and N. J. ZVAIFLER (*Georgetown University Medical School, U.S.A.*)

With the introduction of the Farr ammonium sulphate technique, a more sensitive procedure for the detection of antibodies to deoxyribonucleic acid (DNA) has become available. Published data indicate the usefulness of this technique in the diagnosis of systemic lupus erythematosus (SLE), and also in following the course of this disease. It has been suggested recently that this test is helpful in differentiating SLE from other rheumatic diseases, especially rheumatoid arthritis (Hughes, 1971).

This study presents data on the presence of DNA antibodies in the sera of 62 patients selected by a group of rheumatologists as having unequivocal rheumatoid arthritis. All met the American Rheumatism Association criteria for definite or classical rheumatoid arthritis.

The presence of antibodies to native DNA (nDNA) using the Farr technique was determined, and in addition a titred rheumatoid factor test (Bentonite flocculation test), fluorescent antinuclear antibody (FANA), levels of immunoglobulins A, G, and M, and complement (C3) were also determined. Clinical data were correlated with the laboratory values using a 14×14 matrix and computer-assisted statistical techniques.

The group of 62 patients corresponded well in all

parameters to previously-published series of 'typical' patients with rheumatoid arthritis; 59 of the 62 had DNA-binding values between 0 and 10 per cent, which is considered negative in this laboratory. One patient had 13 per cent binding and two others had values of 19 and 23 per cent respectively. Interestingly, the latter two had negative tests for rheumatoid factor.

These data indicate that antibodies to nDNA are not usually found in patients with 'typical' rheumatoid arthritis, and when found are present in low concentrations only. This is the first presentation of data on the use of this technique in a large group of well-characterized patients with rheumatoid arthritis.

Discussion

DR. D. N. GLASS (*London*) If one standard deviation of the error in your assay for DNA antibodies is 5 per cent, then with a base line of 5 per cent, surely one in 99 sera, i.e. three standard deviations from the mean, could be above 20 per cent binding, assuming a normal distribution of your errors. As you have examined 62 sera, is it possible that your results could be explained by chance? What precautions have you taken to ensure that your 'positive' results represent circulating immunoglobulins specific for DNA?

DR. ROCHMIS Let me preface my answer by saying that much of the vital work on the serum was done in California, and we actually started out using different techniques for detecting DNA antibodies, but discarded them because we felt the Farr technique to be superior. Although in this series of experiments we did not prove the reactant to be immunoglobulin, Farr in his original publications has shown this. In addition, the sera were heat-inactivated, thus eliminating the binding activity of C1q, the other known reactant with DNA. Caesium gradient studies which we performed have shown that 96 per cent of the binding was associated with the native DNA or double-stranded DNA. The error of measurement of the assay in our hands has been calculated to approximate ± 3 per cent of the actual measurement (i.e. not 3 per cent DNA-binding) over the entire range of binding, and it may be even less in the lower ranges. The three elevated values were re-done and fell well within this range.

DR. G. R. V. HUGHES (*Hammersmith*) In our original study of DNA-binding we did find two children with Still's disease who had a very high DNA-binding. Both children subsequently developed florid lupus (Hughes, Cohen, and Christian, 1971). We found no rheumatoid patients with elevated DNA-binding; however, we have recently done a combined study with Dr. Whaley and colleagues in Glasgow on patients with Sjögren's syndrome as part of a study of patients with positive antinuclear factor tests; one or two of these had a slightly abnormal DNA-binding and the rest were normal (Hughes, 1973).

References

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