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Measurement of inflammation

II. Comparison of technetium clearance and thermography with standard methods in a clinical trial

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A number of simple measurements can be used to quantitate the pain and inflammation of rheumatoid arthritis and to demonstrate the effects of treatment (Hart and Huskisson, 1971). Boardman and Hart (1967) introduced a method of testing the anti-inflammatory properties of drugs by measurement of reduction in proximal interphalangeal joint swelling. Two newer methods are now available: technetium (99mTc) clearance and infra-red thermography.

99mTc is an isotope with a short half-life and is therefore safe for repeated administration. It is 90 per cent. protein-bound and passes only slowly into synovial fluid. The size of the effusion does not affect the count rate over a joint (Berry, Browett, Huskisson, Bacon, and Willougby, 1973). Peak count rate over a joint has been used as a measure of inflammation and can be reduced by anti-inflammatory drugs (Dick, Grayson, Woodburn, Nuki, and Buchanan, 1970a; Dick, Neufeld, Prentice, Woodburn, Whaley, Nuki, and Buchanan, 1970b; Collins, Deodhar, Nuki, Whaley, and Buchanan, 1971). Peak count rate for a number of joints can be added to produce a 'technetium index' (Oka, Rekonen, and Ruotsi, 1971), which has been shown to correlate with a clinical index of disease activity. Because it is difficult to give repeated accurate doses of an isotope with such a short half-life, some authors have attempted to correct for dose variations, by counting the syringe before injection, or a blood sample, or an area remote from the inflammation, such as the heart or bladder.

Infra-red thermography produces a coloured photograph of a joint showing the temperature of each area (Cosh and Ring, 1970). Joints in rheumatoid arthritis and other inflammatory arthropathies may be up to 6°C. hotter than the surrounding soft tissues. Several authors have shown in uncontrolled experiments that anti-inflammatory drugs and intra-articular steroids reduce joint temperature, but the method has not been applied to double-blind controlled trials; nor has it been possible to convert the 'photograph' into a measurement. We report a clinical trial in which 99mTc clearance and infra-red thermography were used with standard methods; the experiment was designed to evaluate the newer methods.

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Methods

Six patients in hospital with definite or classical rheumatoid arthritis by the ARA criteria (Ropes, Bennett, Cobb, Jacox and Jessar, 1959) were admitted to the trial; all had active arthritis of both knees. In the first week patients were allowed paracetamol on demand but all anti-inflammatory drugs were stopped. In the 2nd, 3rd, and 4th weeks they received phenylbutazone, placebo, or a drug of unknown activity. Each drug was given for 1 week after which the patients crossed over to another so that every patient received all three drugs. The trial was double-blind but the tablets were made in different shapes and colours to avoid the use of identical formulation. A latin square design was used so that the trial was balanced for treatment order and tablet colour.

At the end of each week the patients were assessed by conventional methods and by 99mTc clearance and thermography. Each measurement was carried out by the same observer, at the same time of day. The observers were not aware of the patient's therapy nor of the results of previous assessments.

Measurements were made of pain, using a visual analogue scale, duration of morning stiffness, paracetamol consumption, articular index (Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieveson, and Buchanan, 1968), and proximal interphalangeal joint size (Boardman and Hart, 1967). In addition, an independent arbirtary assessment was made of the knees, measuring pain, again with a visual analogue scale, and tenderness on pressure, graded as for articular index (Ritchie and others, 1968).

Infra-red thermography was carried out using the Aga

thermovision apparatus in a room kept at a temperature at least 10°C. below skin temperature and constant as far as possible. Variation in ambient temperature during the measurement of a single patient did not exceed 0·5°C. The camera and knee positions were standardized. Each patient was given an intravenous injection of 200 μc. of 99mTc and counts were recorded at half-minute intervals for 30 minutes, with a counter positioned over the patella in contact with the skin surface. At 20 minutes after injection a blood sample was taken and at 30 minutes a count rate was recorded over the opposite knee, both wrists and over the forearm, 2 inches above the wrist. A 99mTc index was calculated by adding the counts for both knees and both wrists. 99mTc clearance was measured in the same way in ten normal volunteers with no history of arthritis.

Results

A. STANDARD METHODS

The conventional assessments consistently showed phenylbutazone as the most effective treatment, the unknown drug second, and placebo third (Table I). Though means of all five assessments gave this result, only the difference in analgesic consumption between phenylbutazone and placebo was statistically significant (Sign test, $P < 0.05$). By any of these assessment methods, at least four of the six patients were as good or better on phenylbutazone as on placebo.

Table I *General assessement of disease activity*

Drug	*Pain score*	*Morning stiffness (min.)*	*Analgesics taken*	*Joint size (mm.)*	*Articular index*
Phenyl-butazone	7·7	63	23·5	568	20·4
Unknown	8·2	89	30·9	571	23·5
Placebo	8·8	95	55·6	573	26·4

The knee assessments gave quite different results (Table II). There was little difference between the effect of phenylbutazone and placebo on pain score. Though this group of patients responded overall, their knees did not necessarily show changes parallel to other joints.

Table II *Assessment of pain and tenderness in the knee*

Drug	*Pain score*	*Tenderness*
Phenylbutazone	10·3	2·5
Unknown	7·9	2·3
Placebo	10·0	3·2

B. THERMOGRAPHY

Table III shows the changes in peak knee temperature and ambient temperature. In the second week of the experiment ambient temperature was a mean of 3·5°C. higher than the other 2 weeks and the mean peak knee temperature was also higher. These differences disappeared when the mean peak temperature for each treatment was considered separately. In this experiment the effect of ambient temperature was greater than that of treatment. The peak knee temperature showed no correlation with any other parameter.

Table III *Effect of treatment and ambient temperature on peak knee temperature*

Temperature (°C.)		*Ambient*	*Peak knee*
Week	1	51·0	32·3
	2	18·5	33·7
	3	15.0	32·5
Drug	Phenylbutazone	16·0	32·2
	Unknown	16·3	32·7
	Placebo	16·3	32·3

An attempt was made to allow for the changes in ambient temperature by expressing the results in relation to the background temperature of the limb away from the knee. All areas above the background temperature were given scores depending on the number of degrees above background. The areas were traced on standard weight paper, cut out and weighed. The four hottest areas were then taken and multiplied by the appropriate correction, the hottest of these by four and the coolest by one, to obtain a composite score. Phenylbutazone and placebo were analysed by this method and the result showed a mean reduction by phenylbutazone of 21 per cent. in the score, which represents the area of maximum temperature. Changes in individual patients showed no correlation with other local measurements. For example, two of the patients showed reductions of 80 and 90 per cent. by phenylbutazone in the area of maximum temperature, though both had as much or more pain and tenderness on phenylbutazone as on placebo.

C. TECHNETIUM CLEARANCE

Uncorrected peak counts for 99mTc clearance were higher in the patients with rheumatoid arthritis than in normal volunteers with some overlap between the groups (Fig. 1). The difference between the groups became much greater when the peak count was corrected for forearm levels and much less when it was corrected for blood levels. This was because the mean forearm levels were lower and mean levels for blood higher in patients with rheumatoid arthritis on placebo then in normal subjects. Drug therapy did not appear to affect this phenomenon. We conclude that 99mTc tends to stay within the vascular compartment in rheumatoid arthritis so that the levels in extracellular fluid are lower; this observation casts doubt upon the validity of dose corrections which use either blood levels or counts over soft tissues.

There was a small reduction in mean uncorrected 99mTc clearance on phenylbutazone compared to

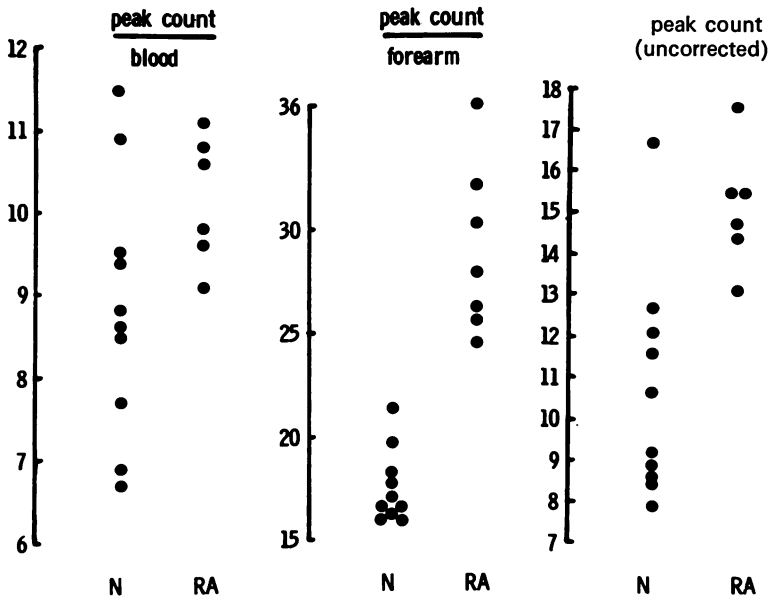

FIG. 1 *Peak 99mTc count for normal and rheumatoid knees, uncorrected and corrected for blood and forearm levels*

placebo (Table IV). Changes in 99mTc clearance, whether uncorrected or corrected for blood or forearm levels, showed no correlation with any other parameter (Fig. 2). The uncorrected 99mTc index, on the other hand, showed a significant correlation with articular index (Fig. 3). The mean 99mTc index also placed the three treatments in the same order as the standard methods (Table IV). Changes in the 99mTc index during the trial did not show a statistically significant correlation with changes in articular index.

Table IV *Effects of treatment on uncorrected peak 99mTc count and on technetium index*

Treatment	*Uncorrected count*	*Technetium index*
Phenylbutazone	14,064	42,009
Unknown	15,389	43,892
Placebo	15,125	44,224

Discussion

Measurement of the anti-inflammatory effects of drugs by reduction in proximal interphalangeal joint swelling is a simple and satisfactory method. Because only a small proportion of patients with rheumatoid arthritis are capable of showing a response, the need exists for a method which would be applicable to all patients and perhaps also to any joint. 99mTc clearance applied to a single joint as used within this trial failed to provide such an advantage. Though other workers have shown that clearance can be dramatically reduced by anti-inflammatory drugs, in this trial the knee joint did not respond by conven-

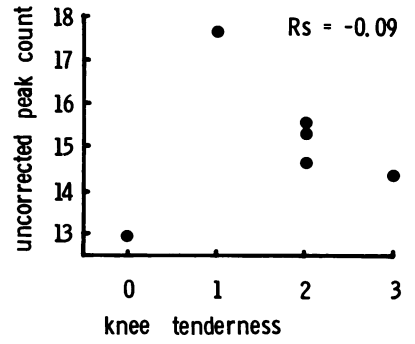

FIG. 2 *Lack of correlation between uncorrected peak 99mTc count and tenderness of the knee*

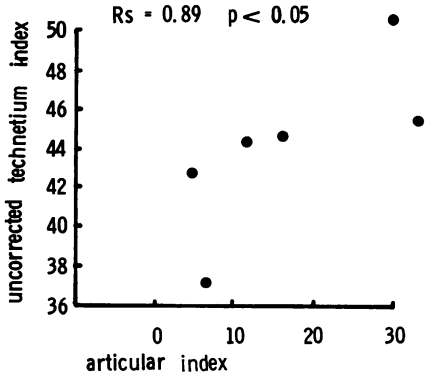

FIG. 3 *Statistically significant correlation between technetium index and articular index*

tional criteria or by 99mTc clearance. For the individual joint, peak 99mTc clearance does not correlate with any other parameter and changes with treatment do not parallel changes in other measurements such as tenderness. On the basis of these results, reduction of technetium clearance by a compound cannot be regarded as synonymous with clinical improvement.

The 99mTc index showed a correlation with the articular index and was a useful measurement in this trial even though changes in individual patients did not correlate with changes in the index. This does not necessarily invalidate the method. Rheumatoid arthritis is a complex disease and different aspects may not correlate with one another. It is a common observation that a single rheumatoid joint may fail to mirror changes in the patient as a whole, and measurement of the single joint is unlikely to be a useful index of anti-inflammatory effects.

Thermography proved to be of limited value in this trial because of the changes in ambient temperature. We suggest that the most satisfactory method of measuring thermographs is to measure the areas of each temperature over a fixed area of joint and compare this with another area away from the joint. This should eliminate the problems of small changes in ambient temperature, currents of air, and relative positions of joint and camera, which are difficult to control.

Summary

In a double-blind crossover trial, the means of standard assessment methods all showed phenylbutazone to be the most effective drug with the unknown drug second, and placebo third, Assessment of the knees in the same patients showed no response.

99mTc clearance studies applied to one knee did not correlate with other parameters, such as tenderness; changes with therapy did not correlate with changes in other parameters. A 99mTc index based on the tenderness of four joints showed a statistically significant correlation with articular index and gave the same overall result as standard methods. The value of these measurements was not increased by correcting them for dose variations using blood or forearm counts and there are reasons for doubting the validity of such corrections.

The measurement of absolute temperature of joints requires a constant ambient temperature; an alternative method is discussed. Changes in joint temperature did not correlate with other parameters in individual patients.

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