Indices of inflammatory activity

Relationship between isotope studies and clinical methods

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Rheumatoid arthritis is still an incurable disease and its management must include the use of non-specific suppressive agents. The great majority of pharmacological agents in this class are drugs of relatively small effect. The difficulty of assessing any such drug is compounded by the spontaneous alterations in activity which are a feature of this disease.

There is no difficulty in detecting major changes in disease activity clinically. However, although many methods of assessment have been studied, no single method has proved entirely satisfactory for the detection of small changes in inflammatory activity, and it is still common practice to employ several methods concurrently (Hollander, Stoner, Brown, and deMoor, 1951; Wright, 1959; Bråneemark, Laine, Lindström, and Vainio, 1963; Co-operating Clinics Committee of the American Rheumatism Association, 1965; McCarty, Gatter, and Phelps, 1965; Boardman and Hart, 1967; Mainland, 1967; Nakamura, Asai, Sonozaki, and Nagano, 1967; Ingpen, 1968; Lansbury, 1968; Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieson, and Buchanan 1968; Goldie, 1969).

Recently radioactive technetium (^{99m}Tc) has been employed as an index of inflammatory activity (Whaley, Pack, Boyle, Dick, Downie, Buchanan, and Gillespie, 1968; Dick, Neufelt, Prentice, Woodburn, Whaley, Nuki, and Buchanan, 1970). This radionuclide is administered intravenously and its accumulation within the joint may be studied by joint scanning (Weiss, Maxfield, Murison, and Hidalgo, 1966) or by external directional counting. Experience with the method is not yet extensive although preliminary reports suggest that differences can be detected between normal and inflamed joints, and that clinical improvement after corticosteroid therapy is reflected by a reduction in maximum or 'peak' uptake of radionuclide by the joint (Dick, Neufelt, and others, 1970).

In this preliminary investigation we have studied the peak uptake of ^{99m}Tc , monitored by external directional counting, in conjunction with a selection

of standard methods of assessment. Any new method of assessment must be shown to work in a relevant clinical situation. We have employed a clinical trial of two widely-used anti-inflammatory agents—sodium salicylate and indomethacin—as a means of assessing the measurement of peak uptake of ^{99m}Tc over the knee joint as an index of inflammatory activity. The sensitivity of this measure was compared with other standard clinical tests and with the rate of disappearance of another radionuclide xenon (^{133}Xe) from the knee joint (Dick, Dick, Nuki, Whaley, Boyle, Shenkin, Downie, and Buchanan 1969; Dick, Whaley, St. Onge, Downie, Boyle, Nuki, Gillespie, and Buchanan 1970; Dick, St. Onge, Gillespie, Downie, Nuki, Gordon, Whaley, Boyle and Buchanan, 1970).

Material and methods

Ten patients with 'classical' rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) took part in a triple cross-over clinical trial over a period of 3 weeks. Four of these patients were men and the six women patients were post-menopausal. The age range was 39 to 58 years. Each patient volunteered to participate in the trial after explanation of its content and implications.

All patients received three successive treatments of a week each on sodium salicylate (Entrosalyl) 5 g./day, indomethacin (Indocid) 100 mg./day, and lactose as placebo, all given as four divided doses in non-identical capsules. The order of treatments administered is summarized in Table I. At the conclusion of each week's treatment the patients were all assessed by the same observer. Each patient was asked general and then specific questions designed to elicit both the efficacy and side-effects of the previous week's treatment. An articular

Table I *Number of patients receiving each treatment in each of three periods*

Treatment	Indomethacin	Sodium salicylate	Placebo
Week 1	2	4	4
2	4	3	3
3	4	3	3

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index (Ritchie and others, 1968) was performed, and measurements were made of grip strength (Wright, 1959) and of the circumference of the finger joints using a millimetre gauge (Boardman and Hart, 1967).

One knee joint, selected for a study at the first assessment on the basis of severity of involvement, was then examined. A history of pain and of stiffness was elicited. The degree of tenderness, measured as the response to firm pressure over the joint margin, was tested and the degree of joint swelling was also subjectively assessed. Grading for each of these four criteria was on a four-point scale where 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.

A narrow-bore needle was inserted into the joint cavity and as much synovial fluid as possible was withdrawn. Approximately 50 μ Ci of ^{133}Xe in 0.5 ml. sterile sodium chloride were injected into the joint cavity and the needle was withdrawn. The wound was sealed with adhesive. A detector incorporating a 1 in. $\times$ 1½ in. thallium-activated sodium iodide scintillation crystal and photomultiplier (EKCO M5400A/1) was positioned over the joint. Immediately afterwards approximately 200 μ Ci of radioactive technetium as per-technetate in solution were injected into a vein in the antecubital fossa. The dose was standardized by the count rate per minute. A double-channel counting system allowed the separate monitoring of ^{133}Xe and $^{99\text{m}}\text{Tc}$ through the same detector. Pulses from the detector were fed through two pulse-height analysers (EKCO 5010), the settings of one being adjusted to the $^{99\text{m}}\text{Tc}$ peak and of the other to the ^{133}Xe peak. Counting was achieved through two ratemeters (EKCO M5183A) and, in the case of $^{99\text{m}}\text{Tc}$, a Kienzle printer. The ^{133}Xe counts were displayed linearly on graph paper by a direct writing pen recorder (Potentiometerschreiber, RE 511).

Counting commenced 3 minutes before the intravenous injection of $^{99\text{m}}\text{Tc}$, and approximately 2 minutes after the intra-articular injection of ^{133}Xe , and was continued for 30 to 45 minutes. The ^{133}Xe graph was sampled at 1-minute intervals and plotted on semi-

logarithmic graph paper as a function of time. A straight line was obtained in each case from which the half-time ($T_{1/2}$) in minutes for the clearance of ^{133}Xe from the knee joint could be obtained. The $^{99\text{m}}\text{Tc}$ print-out was also sampled at 1-minute intervals and plotted linearly as a function of time. Monitoring was continued until a peak count rate for $^{99\text{m}}\text{Tc}$ had been obtained. At the end of each study the count rate over the site of injection of $^{99\text{m}}\text{Tc}$ was compared with that obtained over the equivalent area on the opposite arm. In any study in which a marked discrepancy was found, indicating faulty injection technique, the results from that patient were rejected. Four studies were unsuitable for analysis for this reason.

Patients were asked at the end of the 3 weeks of the trial to give a single preference for one of the three treatments.

Results

The individual values obtained on each treatment are shown in Table II. This trial was in part an attempt to compare different methods of assessing the effect of treatment and Table III shows how consistent were the six techniques employed in each patient. In one patient (No. 3) all six methods indicated that the same treatment was best. In two patients, five of the six methods gave the same result, and in five patients the results of four of the six methods coincided. Thus, in eight out of ten patients, at least four of the six assessment techniques gave the same answer. Of the individual methods, the articular index and the radiotechnetium test corresponded to this answer in all eight patients, whilst the xenon clearance test differed from this in two, and joint sizes corresponded in only three of the eight patients.

Also shown in Table III are the decisions which each patient made as to the single most effective

Table II *Individual results obtained for each patient with each method of assessment*

Patient no.	Articular index			Knee score			Joint sizes (mm.)						Grip strength (mm. Hg)						^{133}Xe Clearance $T_{1/2}$ (min.)			$^{99\text{m}}\text{Tc}$ peak (counts/min.)		
	I S P			I S P			I		S		P		I		S		P		I S P			I S P		
	I	S	P	I	S	P	L	R	L	R	L	R	L	R	L	R	L	R	I	S	P	I	S	P
1	28	30	46	3	4	10	48	42	44	44	65	60	80	60	90	65	50	30	39	23	18	12,700	18,000	16,500
2	5	3	28	6	7	8	46	48	40	41	49	52	60	46	30	40	60	40	23	38	33	8,700	6,500	19,300
3	13	66	62	2	11	10	48	42	62	60	60	58	50	80	20	40	10	30	60	26	22	12,600	47,000	46,000
4	30	14	38	9	5	11	60	50	45	42	55	50	110	80	70	90	60	100	50	68	36	9,400	6,200	11,500
5	17	3	29	3	1	6	40	46	42	44	42	44	70	80	60	80	40	50	49	50	53	13,600	12,200	32,000
6	20	33	40	4	9	11	48	53	48	53	46	55	75	60	45	80	65	70	60	28	26	28,500	33,000	45,500
7	18	28	38	8	8	8	46	52	40	50	49	58	65	20	80	30	90	30	18	20	22	22,000	26,000	30,000
8	13	2	31	6	1	9	36	38	36	44	38	42	90	120	110	100	40	70	25	20	19	17,300	15,600	24,500
9	56	50	60	7	6	9	55	58	63	65	61	63	15	15	20	35	10	15	34	30	18	17,400	16,300	18,000
10	15	28	42	5	8	10	58	46	62	42	46	44	90	110	60	55	45	55	28	26	20	12,400	31,300	43,800

Key: I = Indomethacin; S = Salicylate; P = Placebo; L = Left; R = Right.

Table III Consistency of results obtained by each method of assessment in each patient and patients' overall preferences

Patient no.	Articular index	Knee score	Joint size	Grip strength	$^{133}\text{Xe } T_{1/2}$	^{99m}Tc peak count	Consistency of assessment methods	Patient's preference
1	I	I	I = S	S	I	I	4/6 best on I	I
2	S	I	S	I	S	S	4/6 best on S	S
3	I	I	I	I	I	I	6/6 best on I	I
4	S	S	S	I	S	S	5/6 best on S	S
5	S	S	I = S = P	I	I = S = P	S	Inconsistent	No decision
6	I	I	I = S = P	Opposite results each hand	I	I	4/6 best on I	I
7	I	I = S = P	S	P	P	I	Inconsistent	P
8	S	S	I	S	I	S	4/6 best on S	S
9	S	S	I	S	I	S	4/6 best on S	S
10	I	I	P	I	I	I	5/6 best on I	I

Key: I = Indomethacin; S = Salicylate; P = Placebo.

treatment. In eight of the ten patients this decision reflected the majority preference indicated by the assessment methods. One patient (No. 7) selected the placebo as the single most effective treatment and in that patient the assessment methods were totally discordant. In the final patient (No. 5), who was unable to select a single most effective treatment, three out of the six methods of assessment suggested that salicylate was best. These were the articular index, kneescore, and peak ^{99m}Tc count rate.

The results were further analysed statistically. Each of the six methods of assessment was considered separately, using analysis of variance techniques to decide whether there were significant differences in value of any of the methods when the patients were given the three treatments. As shown in Table I, the triple cross-over design in ten patients did not produce a balanced design. This was due in part to the rejection of results of ^{99m}Tc studies, and two patients started on indomethacin whilst four each started on salicylate and placebo. The statistical method used took account of this imbalance in the design. Dummy variables (Quenouille, 1953) were used to test salicylate against indomethacin (d_1) and placebo against active drugs (d_2).

These two comparisons were chosen to be orthogonal and form together the total variance between treatments. Table IV describes the values assigned to d_1 and d_2 . Analyses of covariance were performed separately for each of the six assessment criteria using the dummy variables and separating

out the effects due to patient variation and to period effect, leaving a residual variation measuring treatment effect alone. Regression coefficients b_1 and b_2 measuring true treatment effects of d_1 and d_2 were determined and their significance tested in the analysis of variance. A two-tailed significance level was assigned to each drug comparison by using the square root of the F-ratios obtained in the regression analyses and entering tables of Student's 't' with 16 degrees of freedom. Table V (overleaf) shows an example of one analysis, using the figures for articular index.

Table VI shows the significance levels obtained by these analyses. Also shown in Table VI are the overall mean values for each assessment method, corrected for period effect by the use of the relevant regression coefficients.* It can be seen that, for the comparison of placebo versus active drugs, all the parameters except joint size showed a significant improvement in favour of the active drugs. This was more marked for the measurements of articular index ($p < 0.001$), knee score, and technetium peak count ($p < 0.005$), whilst grip strength reached a significance of $p < 0.01$ and xenon clearance times reached $p < 0.05$. The tests of indomethacin versus salicylate did not reach conventional statistical significance for any of the parameters, although the technetium peak count came near to this at $p \approx 0.1$. With the exception of joint size, however, the mean

* Indomethacin: corrected mean = overall mean - b_1 - b_2
 Salicylate : corrected mean = overall mean + b_1 - b_2
 Placebo : corrected mean = overall mean - $2b_2$

Table IV Values assigned to dummy variables used in analyses of covariance

Dummy variable	Values assigned with each drug given			Comparison tested
	Salicylate	Indomethacin	Placebo	
d_1	+ 1	- 1	0	Salicylate against indomethacin
d_2	- 1	- 1	+ 2	Placebo against active drugs

Table V *An example of the analysis employed. Figures relate to values obtained with articular index (A I)*

Source	Degrees of freedom	Sum of squares				
		(A I) ²	A I × d ₁	d ₁ ²	A I × d ₂	d ₂ ²
Patients	9	5,073	0	0	0	0
Periods	2	179	4.1	0.6	4.1	0.6
Residual	18	4,031	37.9	19.4	351.9	59.4
Total	29	9,283	42.0	20.0	356.0	60.0

Source	Degrees of freedom	Sum of squares	Mean square	F-ratio	Significance
Due to d ₁	1	74.0	74	0.6	N.S.
Due to d ₂	1	2,083.2	2,083	17.8	p < 0.001
New Residual	16	1,874.0	117		
Old Residual	18	4,031			

Table VI *Corrected mean values obtained with each method of assessment, while patient received indomethacin, salicylate, and placebo. Significance tested using Student's 't' with 16 degrees of freedom (t₁₆)*

Method of assessment	Corrected mean scores			Significance tests			
	Indomethacin	Salicylate	Placebo	Placebo v. active drugs		Indomethacin v. salicylate	
				t ₁₆	p	t ₁₆	p
Articular index	21.6	25.5	41.3	4.2	< 0.001	0.8	≅ 0.4
Knee score	5.3	6.0	9.2	3.7	< 0.005	0.5	≅ 0.6
Joint size	48.6	48.0	51.6	1.7	≅ 0.1	0.2	≅ 0.8
Grip strength	68.2	60.1	48.2	3.0	< 0.01	1.3	≅ 0.2
Xenon T _{1/2}	38.2	33.0	26.9	2.1	≅ 0.05	1.0	≅ 0.3
^{99m} Tc peak counts	15,400	21,200	28,700	3.5	< 0.005	1.7	≅ 0.1

scores for all the methods on indomethacin treatment were better than those on salicylate.

Further analyses were made to compare placebo against each of the two active drugs individually. This was done by forming a set of t-tests derived from the residual mean squares (σ^2) in each analysis of covariance, using the value $\sqrt{2\sigma^2/n}$ as the standard

error of the difference between the means, where n = the number of patients on which each mean score was based. Table VII shows these results. Indomethacin was shown to be significantly better than placebo by all the methods except joint size, with xenon clearance times the least significant of the five. Salicylate was better than placebo accord-

Table VII *Mean differences and significance of difference between values obtained for each assessment method when each active drug was compared individually with placebo*

Method of assessment	Mean differences		σ^2	$\sqrt{2\sigma^2/10}$	Significance tests			
	P—I	P—S			t ₁₆		t ₁₆	
					P—I	p	P—S	p
Articular index	19.7	15.8	117	4.8	4.1	< 0.001	3.3	< 0.005
Knee score	3.9	3.2	6.2	1.11	3.5	< 0.005	2.9	≅ 0.01
Joint size	3.0	3.6	24.7	2.23	1.3	≅ 0.2	1.6	< 0.2
Grip strength	20.0	11.9	187	6.1	3.3	< 0.005	2.0	< 0.1
Xenon T _{1/2}	11.3	6.1	120	4.9	2.3	< 0.05	1.2	< 0.3
^{99m} Tc peak counts	13,300	7,500	58,350,000	3,420	3.9	< 0.005	2.2	< 0.05

Key: P = Placebo; S = Salicylate; I = Indomethacin.

ing to articular index, knee score, and technetium peak count, but no significant difference was shown using joint size, grip strength, or xenon clearance times.

Discussion

It is notoriously difficult to detect small changes in inflammatory activity reliably and reproducibly (Beecher, 1959). Many methods of assessment have been investigated, including both clinical and laboratory measurements.

The availability of gamma-emitting radionuclides has extended the techniques available for the study of joint inflammation *in vivo*. The rate of clearance of a freely diffusible lipid soluble radionuclide of small molecular weight injected into the joint provides a measure of tissue perfusion (Dick, St. Onge, and others, 1970) and is thus a measure of only one aspect of the total inflammatory response. On the other hand, the local accumulation of intravenously administered radioactive technetium (^{99m}Tc) has been shown to reflect tissue volume, vascularity, and, to some extent, synovial fluid volume. (Whaley and others, 1968; Green and Hays, 1969). Thus, although less precise, this technique holds more promise as an index of the overall inflammatory process.

In the present clinical trial we have studied the results obtained by two new methods of assessment, in conjunction with previously established methods. The results clearly show that the ^{133}Xe clearance method offers at best only poor discrimination when compared with standard clinical methods, as has been noted previously (Dick and others, 1969). Thus, although a difference at the 5 per cent. level of significance was demonstrable between placebo and active drug therapy by this technique, the standard methods (articular index, knee score, and grip strength) distinguished the effects of treatment at the 1 per cent. level or better. Since the xenon clearance time reflects tissue perfusion alone (Dick, St. Onge, and others, 1970), which is only one feature of the total inflammatory response, this result is not altogether surprising.

The change in joint circumference provided even poorer discrimination than did the results of the xenon studies. Although joint size has been shown to change with adequate anti-inflammatory therapy by some workers (Boardman and Hart, 1967), alteration attributable to drug effect has been less obvious in other clinical trials (Pitkeathly, Banerjee, Harris, and Sharp, 1966). There are many possible explanations for this discrepancy. Most of the joint swelling in the patients in this study represented irreversible change and probably could not be

modified by short term anti-inflammatory therapy.

On the other hand, the simple determination of peak count rate after an intravenous injection of a measured dose of radioactive technetium seems to offer an index which more closely mirrors clinical change. Thus, the same order of levels of significance achieved when active therapy was compared with placebo by means of the articular index ($p < 0.001$), knee score ($p < 0.005$), and grip strength ($p < 0.01$) was also seen with the technetium peak count rate ($p < 0.005$). Furthermore, the technetium peak count rate gave the same treatment preference as did the articular index for all ten patients, and both these measures corresponded to the majority trend in the eight patients showing consistent results (Table III), whilst the xenon clearance test fell short of this.

In eight of the ten patients the result by the radio-technetium peak count rate agreed with the patients' own treatment preference. Criticism may be levelled at the use of patient preference in a trial which is not blind, but the high level of agreement of the patient's choice with both subjective and objective measurements in this study (Table III) provides some support for its inclusion.

The mean scores (Table VI) for technetium peak count, articular index, knee score, and grip strength all showed better values on indomethacin than on salicylate, and although none of the parameters showed a statistically significant difference the nearest approach to this was the technetium peak count ($p \approx 0.1$). Although most authorities consider indomethacin and aspirin in these doses to be roughly equipotent (Sunshine, Laska, Meisner, and Morgan, 1964; Pitkeathly and others, 1966; Pinals and Frank, 1967), there is some evidence to suggest that indomethacin exerts a more powerful anti-inflammatory effect than aspirin (Gáspárdy, Gáspárdy, Bálint, and Kemény, 1966). The trend of the findings in the present study agree with this.

The results of this small but objective study therefore show that the measurement of peak count rate of radioactive technetium is capable of demonstrating anti-inflammatory effect in a short-term clinical trial of non-steroidal anti-inflammatory drugs. The direction and the degree of change of this measurement compare favourably with results obtained by other clinical methods.

Summary

Ten patients with classical rheumatoid arthritis entered a triple cross-over clinical trial of anti-inflammatory treatment using sodium salicylate 5 g./day, indomethacin 100 mg./day, and placebo, each treatment being administered for one week. Six methods of assessment were used, including an

articular index, joint size, grip strength, a knee score, and two new methods of assessment derived from isotope studies. Peak uptake by the knee after the intravenous administration of radioactive technetium and the half-life of intra-articularly injected

xenon were determined each week. The articular index, grip strength, knee score, and radiotechnetium peak count rate discriminated change in the inflammatory process as a result of treatment better than did joint size or xenon clearance measurements.

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