

Measurement of joint inflammation

A radioisotopic method

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Radioactive technetium (^{99m}Tc) has been employed in the study of many organs (Harper, Andros, and Lathrop, 1962; Andros, Harper, Lathrop, and McCardle, 1965; Degrossi, Gotta, Olivari, Pecorini, and Chwojnik, 1965; Larson and Nelp, 1965; Davis, Alexander, Witcofski, and Maynard, 1966; Harden, Alexander, and Kennedy, 1967; Irvine, Stewart, McLoughlin, and Tothill, 1967; Tothill and Irvine, 1967).

Technetium photoscans (Weiss, Maxfield, Murison, and Hidalgo, 1966) of the joint have been shown to reflect the degree of inflammatory involvement at the time of study and a method of quantitating such scans has been described (Whaley, Pack, Boyle, Dick, Downie, Buchanan, and Gillespie, 1968). The photoscan display system yields a picture of isotope content of the area over a relatively short period of time, however, and the method of quantitation is tedious. Furthermore, a dose of the order of one millicurie of the isotope is required to achieve optimum scans. This is a major disadvantage when repeated measurements are necessary, for example, in clinical trials of therapeutic agents.

We considered that continuous external directional counting over the knee joint after the intravenous administration of ^{99m}Tc might overcome these difficulties. Thus, we hoped to derive more information from the pattern of uptake than was afforded by a single photoscan and we anticipated that a much lower dose of the isotope would be required. Finally, we hoped that this method would prove simpler to quantitate than the photoscan method.

Material and methods

PATIENTS

Studies were performed on twenty clinically active knee joints of patients with 'classical' rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959). The mean age of the patients was 52.8 years (range 42 to 65), and five were male.

In five patients repeat studies were performed after 24 hours to determine the day-to-day reproducibility of the method, and a further six patients received prednisolone ('Ultracortenol' 10 mg.) intra-articularly. The study was then repeated one week later.

Isotope studies were performed on eight healthy male volunteers aged between 20 and 28 years (mean 24.4), none of whom gave a history of disease or trauma to the knee joint. The isotope studies were repeated after 24 hours in two of these subjects to determine the day-to-day reproducibility.

Clinical assessment of the knee joint was performed by the same observer before each isotope study. A history of pain or stiffness was elicited and graded. The knee was then subjected to firm pressure over the joint margin and the response graded. Finally the degree of swelling was estimated subjectively and graded. Grading was on a 0 to 3 basis: 0 = 'absent'; 1 = 'slight'; 2 = 'moderate'; and 3 = 'severe'. Thus the maximum score for any individual joint was +12.

ISOTOPE STUDIES

The patient reclined comfortably in bed and the knee was immobilized during the study.

One millicurie of ^{99m}Tc in 5 ml. sterile NaCl was obtained daily at noon, and studies were performed between noon and 4.00 p.m. because of the short half life of the isotope (6 hrs).

ISOTOPE STUDIES

Approximately 200 μci (standardized by count rate) of ^{99m}Tc in 1 ml. NaCl were administered intravenously into a vein in the antecubital fossa. In early feasibility studies it had been noted that excess counts were frequently present over the injection site when compared with the identical area on the opposite arm at the conclusion of the study. Accordingly great care was taken to ensure that the injection was truly intravenous.

A collimated 1×1.5 " thallium-activated sodium iodide crystal connected through an Ecko ratemeter (M5 180) and pulse height analyser (M5 010) to a KIENZLE automatic print-out was positioned directly over the patella touching the skin. Counts per 60 sec. were taken with counting conditions adjusted for ^{99m}Tc ; counting was begun 120 sec. before the injection and continued until the count rate was declining. The results obtained were plotted on graph paper and the peak count rate and time to reach the peak were read from the graph.

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Results

These are shown in Tables I, II, and III (overleaf).

The peak values obtained in the normal subjects

(Mean $9,300 \pm \text{S.E.M. } 987$ counts per min.) were significantly lower ($P < 0.001$) than those in the rheumatoid patients (Mean $17,140 \pm \text{S.E.M. } 1,871$ counts per min.).

The time to reach the peak in the normal subjects (Mean $24.6 \pm \text{S.E.M. } 3.54$ min.) did not differ significantly ($P < 0.2 > 0.1$) from that in the rheumatoid patients (Mean $15.8 \pm \text{S.E.M. } 5.33$ min.).

Table II shows the results obtained in the two normal subjects and the five rheumatoid patients in whom the isotope studies were repeated 24 hrs later. The standard error of the difference was 222 counts per min. for the peak values.

Table I Normal and rheumatoid subjects compared

Normal		Rheumatoid arthritic	
Peak counts per min.	Time to reach peak (min.)	Peak counts per min.	Time to reach peak (min.)
8,900	18	28,000	16
13,100	16	23,000	13
5,700	23	18,000	5
11,800	47	16,800	20
7,500	22	10,100	10
9,300	30	6,400	33
6,100	18	14,000	18
12,000	12	13,400	22
		19,900	9
		7,900	9
		9,300	31
		10,300	15
		5,000	23
		26,400	6
		30,000	13
		12,000	15
		34,900	18
		19,500	20
		24,000	13
		14,000	8
Mean 9,300	24.6	17,140	15.8
S.E.M. 987	3.54	1,871	5.33

Time to reach peak in rheumatoid compared with normal subjects $P < 0.2 > 0.1$

Peak counts in rheumatoid compared with normal subjects $P < 0.001$

The results of the isotope studies and clinical knee assessments before and after the intra-articular injection of prednisolone are shown in Table III. The means of the peak values and clinical knee assessments before the injection (Mean $18,466 \pm \text{S.E.M. } 3,014$ counts per min. and Mean $7 \pm \text{S.E.M. } 1.13$ respectively) differ significantly ($P < 0.05 > 0.01$ and $P < 0.05 > 0.01$ respectively) from the means of the same parameters one week after the injection (Mean $9,283 \pm \text{S.E.M. } 1,499$ counts per min. and Mean $3.3 \pm \text{S.E.M. } 2.07$ respectively). The mean values of the time taken to reach the peak before the injection of prednisolone (Mean $16 \pm \text{S.E.M. } 3.41$ min.) did not differ significantly ($P > 0.35$) from those obtained one week after the injection (Mean $14.6 \pm \text{S.E.M. } 1.09$).

Discussion

The results show that there is a significant difference between the peak uptake of ^{99m}Tc by the rheumatoid knee joint when compared with the normal joint. It is likely that this reflects the increased amounts of blood, synovial tissue, and synovial fluid in the rheumatoid joint. Although these studies were per-

Table II Results obtained when peak counts were measured in seven subjects on two occasions at an interval of 24 hrs

Subjects	Peak counts per min.	
	1st Occasion	2nd Occasion
Normal	6,300	6,400
	6,400	5,800
Rheumatoid arthritis	13,000	12,700
	12,700	13,100
	25,000	23,900
	18,000	17,700
	32,000	32,600

Standard error of the difference 222 counts per min.

Table III Values obtained for knee score, peak counts, and time to reach peak in six patients before, and one week after intra-articular injection of prednisolone

Patient no.	Before prednisolone			After prednisolone		
	Knee score	Peak counts per min.	Time to reach peak (min.)	Knee score	Peak counts per min.	Time to reach peak (min.)
1	9	22,000	14	3	6,000	13
2	9	10,800	18	1	9,600	12
3	7	14,000	31	4	12,000	14
4	6	19,900	6	5	4,600	13
5	9	30,800	12	1	9,000	18
6	2	13,300	15	6	14,500	18
Mean	7	18,466	16	3.3	9,283	14.6
$\pm \text{S.E.M.}$	1.13	3,014	3.41	2.07	1,499	1.09

Knee score before compared with after prednisolone $P < 0.05 > 0.01$
 Peak counts before compared with after prednisolone $P < 0.05 > 0.01$
 Time to reach peak before compared with after prednisolone $P > 0.35$

formed on the knee joint, there is no reason why ^{99m}Tc uptake should not be used in the study of other joints.

In early feasibility studies, it was noted that in many cases, despite no obvious fault in the injection technique, a significant proportion of the administered dose remained at the injection site. In the most obvious cases this was manifest in the results by a very slow rise to peak count rate. To obviate this problem great care is required when administering the isotope, and the injection site should be monitored after each study.

Provided care is taken these isotope studies would seem to possess an acceptable degree of reproducibility. The standard error of the difference of the repeat isotope studies was 222 counts per min. for the peak uptake.

It may be possible to use the uptake of ^{99m}Tc by the joint to measure the anti-inflammatory effect of drugs. Thus the ^{99m}Tc peak uptake paralleled the clinical knee assessment when the joint was subjected to an intra-articular injection of prednisolone. The dose of the isotope used in this study ($200\ \mu\text{Ci}$) is low enough to allow repeat studies, and indeed, considering the counts obtained with this dose, it

would appear that it may be possible to reduce the dose even further.

It is not possible at this time to allocate priorities to the various parameters of the uptake pattern, but studies are in hand to this purpose. It would also seem that the localization of the isotope within the joint is worthy of further study and this is in progress.

Thus the pattern of uptake of intravenously administered ^{99m}Tc by the joint may be useful in the study of joint inflammation and in evaluating the anti-inflammatory effect of drugs.

Summary

A method for the measurement of joint inflammation based upon the rate of uptake of ^{99m}Tc by the joint is described. The method is reproducible and shows differences between normal and diseased joints. It has been shown to be capable of reflecting the effect of anti-inflammatory therapy.

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RÉSUMÉ

Le mesurage de l'inflammation articulaire Une méthode radio-isotope

Une méthode pour mesurer l'inflammation articulaire basée sur le taux de l'absorption de ^{99m}Tc par l'articulation est décrite. La méthode peut être reproduite et montre les différences entre les articulations saines et malades. Il a été démontré qu'il est possible par cette méthode de reproduire l'effet de la thérapie antiinflammatoire.

SUMARIO

Medición de la inflamación de articulaciones Método de radioisótopos

Se describe un método para medir la inflamación de articulaciones, basado en la velocidad de absorción de ^{99m}Tc , por la articulación. El método se puede repetir y muestra diferencias entre articulaciones normales y enfermas. Se ha mostrado que es capaz de reflejar el efecto de la terapia antiinflamatoria.