INTRA-ARTICULAR THERAPY IN OSTEO-ARTHRITIS COMPARISON OF HYDROCORTISONE ACETATE AND HYDRO- CORTISONE *TERTIARY*-BUTYLACETATE

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The intra-articular injection of hydrocortisone acetate is commonly used in the treatment of osteo-arthritis, although its action in this disease has received less careful study than in rheumatoid arthritis. In 1955 a less soluble ester, hydrocortisone *tertiary*-butylacetate (TBA) was developed for intra-articular therapy with the claim that its effects were more pronounced and of longer duration (Hollander, Brown, Jessar, Udell, Smukler, and Bowie, 1955).

The purpose of the present trial was to evaluate both drugs in the treatment of osteo-arthritis by a double-blind, crossover method. Each patient received both compounds as well as placebo and thus served as his own control. This formed part of a wider study of the value of intra-articular therapy in rheumatic disease. The results of the present investigation will be compared with those obtained in rheumatoid arthritis (Chandler, Wright, and Hartfall, 1958).

Design of Trial

25 patients whose main complaint arose from osteo-arthritis of the knees were included in the trial. In thirteen both knees were treated, and in twelve only one knee, giving a total of 38 joints suitable for trial. No patient had received intra-articular therapy within 2 months of the start of the trial. Symptomatic treatment remained constant throughout the period of study which was conducted under out-patient conditions.

The trial consisted of three courses of treatment (hydrocortisone acetate, TBA, and placebo) each of four fortnightly injections, with 8 weeks rest between treatments. Dosages of TBA and hydrocortisone were 25 mg. in 1 ml. fluid. The placebo (1 ml.) was the vehicle used as the suspending and preserving agent for the active compounds. The order of courses in each patient was randomized from a master sheet in which names were entered consecutively.

The fortnightly assessments comprised the following measurements:

- Walking time over 75 yards;
- Range of joint movement and limitation of extension determined by a goniometer;
- Tenderness (graded 0 = none, 1 = slight, 2 = definite, 3 = wincing, 4 = withdrawal and/or exclamation);
- Pain (graded 0 = none, 1 = slight on walking, 2 = marked on walking, 3 = mild at rest, 4 = severe at rest).

Radiographs of the knees were obtained before and after the trial.

Results

Three patients failed to complete the trial; two defaulted after the second course of injections, and one developed an unrelated disease after the third injection of the second course. This resulted in five knees not receiving a course of placebo injections.

The specific data (walking time, etc.) derived from the first assessment in each treatment period were compared with the same measurements made at the four assessments in the succeeding 8-week rest period. Changes in walking time and joint movement were estimated as a percentage of the pre-treatment measurements; changes in limitation of extension were calculated as a percentage of maximal joint range (145°). Although pain and tenderness were graded at each assessment, because this parameter is entirely subjective, differences were calculated on the basis of improvement and no improvement. In this way the effect of treatment, both immediate and sustained, was calculated for each knee for each of the three treatments. The mean change for each of the three groups (hydrocortisone, TBA, and placebo) between pre-treatment assessments and each of the four post-treatment assessments was analysed by conventional statistical methods.

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Pain.—At the second week after the course of injections a greater proportion of the knees receiving hydrocortisone and TBA improved than did those receiving the placebo (Table I). The response to TBA was significantly better than that to the placebo ($P < 0.02$), but the greater improvement following hydrocortisone when compared with placebo did not achieve the level of significance ($P < 0.3$).

TABLE I
EFFECT ON PAIN OF HYDROCORTISONE, HYDROCORTISONE TBA, AND PLACEBO AT THE SECOND WEEK AFTER THE COURSE OF INJECTIONS

Result	Injection		
	Hydrocortisone	TBA	Placebo
Improvement ..	19	25	12
No improvement ..	19	13	21
Total Knees ..	38	38	33

There was no significant difference between the response to the two active drugs ($P < 0.2$). At subsequent assessments there was no significant difference between the response to any of the injections.

Other Parameters.—No significant improvement in walking time, range of movement, limitation of extension, or tenderness was apparent after the injection of the two drugs compared with placebo.

Advantage of First Treatment

It has been suggested that, irrespective of the nature of the substance injected, the first course of injections given to a patient with rheumatoid arthritis will produce subjective improvement (Fearnley, Lackner, Meanock, and Bywaters, 1956). This possibility was therefore studied by comparing the improvement following the first course of injections with that following the second and third courses which were grouped together for purposes of analysis (Table II).

TABLE II
COMPARISON OF EFFECT OF FIRST COURSE OF INJECTIONS WITH EFFECT OF SUBSEQUENT COURSES

Mobility	Mean Improvement			P
	First Course	Subsequent Course	Standard Error of Mean Difference	
Walking Time (per cent. of patients) ..	9.5	1.1	± 2.42	$< 0.01^*$
Range of Movement (per cent. of knees) ..	3.74	1.76	± 1.17	< 0.1
Limitation of Extension (per cent. of knees) ..	0.8	0.28	± 0.86	< 0.6

* Significant difference.

Only with walking time did the first course of treatment show a significant advantage over subsequent treatments. Here the difference was very striking. The mean improvement after the first course was 9 per cent. compared with 1 per cent. after subsequent courses. The difference is highly significant ($P < 0.01$).

The improvement 2 weeks after the first injection of the first course was then compared with the improvement 2 weeks after the second injection of that course. There was no significant difference between the effect of the first and the second injection.

Complications

In two knees there was increased pain and stiffness lasting 2 and 3 days respectively after the injection of TBA. One patient complained of swelling of the ankle on two occasions after the injection of TBA, but no abnormality was seen at his next visit to the clinic.

Radiological Changes

Radiographs of each injected knee (anteroposterior and lateral) were taken at the beginning and end of the trial. The x-ray appearances were graded into four categories for osteo-arthritis (Kellgren and Lawrence, 1957):

- 1 = doubtful,
- 2 = minimal,
- 3 = moderate,
- 4 = severe.

In addition, the films were examined for evidence of osteoporosis and erosions. The initial films showed one knee with Grade 1 changes, nine with Grade 2, 21 with Grade 3, and seven with Grade 4. No deterioration in the osteo-arthritic lesions was seen during the period of the trial. Osteoporosis and erosions did not develop in any joint.

Discussion

Previous Reports.—Local injection into an involved joint has long been practised as a useful adjunct in the treatment of rheumatic diseases. It has many advantages, particularly in that systemic complications do not occur. Hollander, Brown, Jessar, and Brown (1951) first used hydrocortisone acetate for intra-articular injection, and the drug has since come to be generally regarded as beneficial in the treatment of rheumatoid arthritis and osteo-arthritis. However, controlled trials of its value have been few, and most reports have dealt with the authors' experience in retrospect. Moreover, in many reports, little distinction has

been made in analysis between the results in patients with rheumatoid arthritis and those in patients with osteo-arthritis (Hollander and others, 1951; Duff, 1956; Zuckner, Machek, and Ahern, 1956; Bonner, 1959). In a strictly controlled study (Chandler, Wright, and Hartfall, 1958), it was demonstrated that both hydrocortisone acetate and its *tertiary*-butylacetate derivative had a significant advantage over a placebo in the treatment of the knees of patients with rheumatoid arthritis. Improvement was generally greater and of longer duration with TBA than with hydrocortisone, but the difference was not significant.

Even greater value has been claimed for both these agents in osteo-arthritis (Hollander and others, 1951; Desmarais, 1952; Hollander and others, 1955; Zuckner, Machek, Caciolo, Ahern, and Ramsey, 1958). Williams (1958) claimed that TBA was effective over a longer period than hydrocortisone, but Kehr (1959) could detect no difference.

In the present study the response to treatment with respect to pain and tenderness has been classed as improved or not improved.

It was felt that to apply statistical methods to numbers assigned for grades of pain and tenderness would be merely to cover an edifice of inaccuracy with a coat of scientific paint. On these criteria the only significant improvement obtained from the active compounds was that in respect of pain; 2 weeks after the injection of both drugs less pain was experienced than after the placebo, and this was statistically significant ($P < 0.02$) in the case of TBA. There was no significant difference between the active drugs. At the fourth and subsequent weeks after injection, however, neither drug conferred any significant advantage over the placebo. The effect of TBA although significant was transient. The fact that the improvement following hydrocortisone was not significant at the second week suggests that its effect is even more short lived than that of TBA.

The benefit derived from these drugs was therefore much less marked than that previously obtained under similar conditions in patients with rheumatoid arthritis who improved in all criteria of assessment for periods of 2 to 8 weeks. Nor do our findings accord with the majority experience (Hollander and others, 1951; Desmarais, 1952; Williams, 1958; Kehr, 1959); yet the results are not unexpected in view of the fundamentally different pathology of the two diseases. It is to be anticipated that the inflammatory arthritis of rheumatoid type would show a better response to steroid therapy, either local or systemic, than the purely degenerative

lesion of osteo-arthritis. The difference between our experience and that of others in the local treatment of osteo-arthritis may reflect only the failure of other authors to conduct trials under controlled conditions. Miller, White, and Norton (1958), in a careful study of 181 patients with osteo-arthritis of the knees, were unable to detect any difference in response to the injection of lactic acid, novocaine, hydrocortisone, and saline. However, the first assessment following treatment was made 6 weeks after the course of injections, so that a less prolonged effect could not be measured.

Effect of Order of Injection.—Fearnley and others (1956), in a pilot study of intra-articular procaine and hydrocortisone acetate in rheumatoid arthritis, found that the first course of treatment conferred more benefit than the second, regardless of which drug was used. In this study of patients with osteo-arthritis this was evident in the effect on walking time. The percentage improvement in walking time after the first course was nine times greater than that after subsequent courses. Claims for improvement from single courses of treatment must therefore be evaluated cautiously in the light of this observation.

Placebo Response.—It was of interest that, although more patients experienced relief of pain after injection of the active compounds than after that of the placebo, in 36 per cent. of knees there was improvement from the inert material. If one-third improves with inactive material, great care must obviously be exercised in interpreting the results of uncontrolled studies of intra-articular therapy. The interesting problem of the placebo reactor has formed the basis of a further study of these patients by Morison, Woodmansey, and Young (1960). After preliminary psychological assessment a course of placebo tablets was given, on which 26 per cent. of patients improved, and 38 per cent. developed side-effects. Those who consistently showed no response to placebo injections or tablets displayed no side-effects from the inert preparations. This work suggests that a substantial reduction in the number of patients likely to benefit from inert preparations could be obtained by a preliminary study using placebo tablets; only those patients showing no side-effects would then be included in the subsequent trial. The group studied would then, of course, be selected. Alternatively, all patients would take part in the trial, which would then include a group of predicted reactors.

Complications.—There were few complications after intra-articular injection. In two knees there

was increased pain and stiffness which lasted 3 days; this local exacerbation has been noted by other workers (Kendall, 1958). In a trial of similar design involving 24 patients with rheumatoid arthritis, three patients developed deep vein thrombosis in the injected leg (Chandler, Wright, and Hartfall, 1958). This complication was not observed in any patient with osteo-arthritis; our experience is that deep vein thrombosis is a complication of rheumatoid disease, and it may be that its development in the injected leg was precipitated by intra-articular injection.

It was noted that, after prolonged intra-articular administration of hydrocortisone in rheumatoid arthritis, radiological deterioration, sometimes considerable, occurred in over half the knees so treated (Chandler and Wright, 1958). The development of relatively painless destruction of the hip joint in four patients treated with corticosteroids has since been described (Sweetnam, Mason, and Murray, 1960). Three of these patients received steroids systemically and one by intra-articular injection. Such deterioration, resembling Charcot's arthropathy, may also occur in osteo-arthritis after multiple (18) injections of intra-articular hydrocortisone (Chandler, Jones, Wright, and Hartfall, 1959), but this has not been our experience in the present trial, in which fewer injections of active compound were used.

Summary

The effect of intra-articular injections of hydrocortisone acetate and hydrocortisone *tertiary*-butylacetate (TBA) has been studied in 25 patients with osteo-arthritis whose main incapacity arose from involvement of the knees.

Each patient was given three courses of injections (hydrocortisone, TBA, and placebo) in random order. Each course consisted of four injections at fortnightly intervals, with 8 weeks' rest between courses. Pain, tenderness, walking time, range of joint movement, and limitation of extension were assessed every 2 weeks.

A transient lessening of pain followed the courses of active compounds, but no other significant benefit was derived. There was no significant difference between the results of the two drugs. Significant improvement in walking time occurred after the first course of treatment irrespective of its nature. Three patients experienced minimal complications. No radiological deterioration was observed in the knees injected.

36 per cent. of the knees improved from the inert material.

In a subsequent assessment of the effect of placebo tablets on these patients, 26 per cent. improved and

38 per cent. developed side-effects. Those consistently showing no response to placebo therapy displayed no side-effects.

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Traitement intra-articulaire dans l'ostéo-arthrite.— Comparaison de l'acétate d'hydrocortisone et du butylacétate tertiaire d'hydrocortisone

RÉSUMÉ

On a procédé à une étude sur l'effet des injections intra-articulaires d'acétate d'hydrocortisone et de butylacétate d'hydrocortisone (TBA) chez 25 malades atteints d'ostéo-arthrite, dont l'incapacité principale siegeait aux genoux.

Chaque malade a reçu, dans un ordre fortuit, trois séries d'injections: hydrocortisone, TBA et une substance inerte. Chaque série consistait de quatre injections bimensuelles, avec huit semaines de repos entre les séries. Toutes les deux semaines on recherchait: douleur spontanée, douleur provoquée à la palpation, temps de marche, amplitude du mouvement articulaire et limites de l'extension.

Une diminution temporaire de la douleur a suivi chaque série d'injections des substances actives, mais on n'a noté aucun autre avantage appréciable. On n'a pas observé de différence appréciable entre les effets des deux composés d'hydrocortisone. Une amélioration appréciable du "temps de marche" s'est produit après la première série d'injections, indépendamment de la substance administrée. Trois malades ont ressenti des complications peu importantes. On n'a pas observé de détériorations radiologiques dans les genoux injectés.

Trente-six pour cent des genoux ont manifesté une amélioration après avoir reçu la substance inerte. Au cours d'une évaluation subséquente de l'effet des comprimés-témoins sur ces malades, on a trouvé que 26 pour cent d'entre eux ont manifesté une amélioration et 38

pour cent des effets secondaires. Les malades qui ne réagissaient jamais thérapeutiquement à ces comprimés de substance inerte, n'accusaient pas d'effets secondaires.

**Terapéutica intra-articular de ósteo-artritis.—
Comparación del acetato de hidrocortisona y
del butilacetato terciario de hidrocortisona**

SUMARIO

Se realizó un estudio sobre el efecto de las inyecciones intra-articulares de acetato de hidrocortisona y de butilacetato terciario de hidrocortisona (TBA) en 25 enfermos con ósteo-artritis, cuya principal incapacidad residía en la afectación de las rodillas.

Cada enfermo recibió, en un orden determinado al azar, tres series de inyecciones: hidrocortisona, TBA y una substancia inerte de control. Cada serie consistió en cuatro inyecciones quincenales, con ocho semanas de descanso entre las series. Cada quincena se investigó: dolor espontáneo, dolor provocado a la exploración,

tiempo caminando, amplitud del movimiento articular y limitación de la extensión.

Una pasajera disminución del dolor siguió a cada serie de inyecciones de compuesto activo, pero no se apreció otro beneficio significativo. No se notó diferencia apreciable entre los efectos de los dos compuestos de hidrocortisona. Una apreciable mejoría del "tiempo caminando" apareció después de la primera serie de inyecciones, independientemente de la substancia administrada. Tres enfermos experimentaron complicaciones mínimas. No se observó agravación de los signos radiológicos en las rodillas inyectadas.

El 36 por ciento de los enfermos aseguraron haber experimentado mejoría con la inyección de substancia inerte. En una investigación posterior del efecto de comprimidos postizos en dichos enfermos, 26 por ciento de ellos manifestó una mejoría y el 38 por ciento efectos secundarios. Los enfermos que repetidamente no presentaron ninguna respuesta terapéutica a estos comprimidos de substancia inerte, tampoco presentaron efectos secundarios.