PILOT STUDY OF INTRA-ARTICULAR PROCAINE
AND HYDROCORTISONE ACETATE IN
RHEUMATOID ARTHRITIS

BY

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For many years the intra-articular injection of procaine, with or without the addition of lactic acid or phosphate, has been advocated in the treatment of both rheumatoid arthritis and degenerative joint disease (osteo-arthritis), but controlled trials have been only rarely conducted. Such results as have been published (Desmarais, 1952) have not indicated any major difference between the solutions used, and it may be that they are in fact all relatively inert. With the introduction of hydrocortisone acetate, clinical and biochemical observations indicated that improvement occurred in a number of patients. Indeed, with cortisone acetate, which seldom produces clinical improvement, statistically significant biochemical improvement, compared with the results of saline injections, was shown to occur in a controlled cross-over trial (Dixon and Bywaters, 1953). It seemed important therefore to assess the practical day-to-day value of hydrocortisone acetate, compared with that of procaine injections for treatment under out-patient conditions, and it was decided to explore the possibilities of a controlled cross-over trial in a small number of co-operative patients. Each patient was to have both treatments and thus to serve as his own control.

Material

Twelve patients with generalized rheumatoid arthritis were selected whose main incapacity could be ascribed to severe involvement of one knee joint. The patient might have a flexion deformity of the severely affected knee, but a range of at least 20° of passive movement was required. The patients had to be co-operative and with a good record of attendance. The erythrocyte sedimentation rate was required to be 20 mm./hr or more (Westergren), indicating some degree of disease activity.

The patient was required to be able to walk at least 50 yards with or without a stick.

The patients were allocated at random into two equal groups; of the twelve initially selected, two fell out because of intercurrent illness, and ten therefore completed the trial, five in each group.

Scheme of Trial

One group received a total of four fortnightly injections of 2·0 ml. (100 mg.) hydrocortisone acetate into the affected knee. This was followed by a rest period of 8 weeks after which each patient in this group received a total of four fortnightly injections of 4·0 ml. 2 per cent. procaine into the same joint. They were then observed for a further 8 weeks. In the other group the same procedure was followed, but in the reverse order.

Fig. 1 (opposite) shows the design of the trial, and the mean erythrocyte sedimentation rate at each attendance of the two groups for the whole period of 28 weeks. The following simple measurements were made initially and at each fortnightly attendance throughout the trial:

- Erythrocyte sedimentation rate (Westergren),
- walking time (time taken to walk 50 yards),
- range of movement of knee (judged by eye),
- limitation of knee extension (judged by eye),
- joint tenderness at the knee (0—no tenderness; 1—patient states joint is tender; 2—patient winces; 3—withdrawal and/or exclamation).

In addition, an assessment was made of functional status in five grades, and joint circumference, quadriceps circumference, and the volume of fluid aspirated were measured on each occasion, but as these criteria showed no important changes they are not included in the reported results.
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Results

The mean measurements at fortnightly intervals for each group are shown in Figs 2 to 5 (overleaf).

Walking Time.—The mean of each group (Fig. 2) shortened during the first course of injections in all patients of both treatment groups. Little change occurred in either group during the rest period (6-14 weeks). In the group receiving hydrocortisone first, the walking time increased somewhat at the end of the first rest period, and this increase, marked in two patients, continued throughout the procaine injections and the second rest period. In contrast, the group receiving procaine first, showed no relapse during hydrocortisone injections or during the subsequent rest period.

Range of Movement.—The changes showed a somewhat similar pattern to that of the walking time (Fig. 3). Both groups showed an increase in range during the first course of injections, whether of procaine or hydrocortisone. The group receiving hydrocortisone first relapsed during the rest period, levelled off somewhat during the procaine injections, and relapsed again during the second rest period. The group receiving procaine first maintained their improvement throughout the remainder of the trial.

Limitation of Extension.—The mean of the two groups is shown in Fig. 4. In the group receiving hydrocortisone first, there was a marked reduction of limitation, followed by a relapse in the first rest period, some further improvement during the procaine injections, and a further relapse during the second rest period. The other group showed slight improvement with procaine, a relapse during the rest period, and moderate improvement with hydrocortisone. It may be that the amount of

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**Fig. 1.**—Design of trial and mean erythrocyte sedimentation rate of each group during the whole 28 weeks (five patients in each group).
possible improvement differed between these two groups.

Joint Tenderness (Fig. 5).—This decreased sharply in the group receiving hydrocortisone, and at first disappeared completely in four out of five. This was followed by a relapse during the first rest period, a levelling off during procaine injections, and a further improvement following the procaine. The group receiving procaine first showed a more moderate improvement which continued during the first rest period and during the hydrocortisone injections.

Combined Measurements.—Fig. 6 (opposite) shows the data in terms of the injections irrespective of group, and illustrates the mean measurements of all patients during the procaine injections, the hydrocortisone injections, and the subsequent rest period. When the results are expressed in this way, it is seen that walking time and range of movement showed comparable improvement with procaine and with hydrocortisone. Limitation of extension was improved by hydrocortisone, but only slightly by procaine, with a relapse during the rest period. Joint tenderness decreased on hydrocortisone and increased again afterwards; there was no response to procaine, but improvement occurred during the rest period after the procaine injections.

The groups are somewhat small for statistical comparisons, and the range of variation from patient to patient is large. Thus, if comparison is made between the change in each individual during the hydrocortisone injections (Week 0 data minus Week 8 data, and Week 14 data minus Week 22...
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Fig. 6.—Comparison of average measurements of all patients combined during the two injection periods and subsequent rest periods.

data) and during the procaine injections, the difference between the average changes for the two drugs in no instance exceeds twice the standard error of that difference and hence is not significant. The criterion which came nearest to significance (a ratio of 1.84) was "limitation of extension". The difference between the two drug groups in the first 8 weeks only, i.e. considering only the first treatment, does not reach levels of significance.

For overall comparison, a weighted score was made for each patient giving approximately equal weight to all the criteria used. This arbitrary score ranged between 219 and 24 points for this group of ten patients. Changes occurring during this first treatment (i.e. in the first 8 weeks) show significant improvement over those occurring during the second treatment (between Weeks 14 and 22), irrespective of the drug used; this gives a difference between the means which is 5.6 times the standard error of the difference. There is no difference between the drugs if they are analysed in the same way. There was only a very slight correlation between the scores achieved by individual patients in the first treatment and those achieved in the second. Thus, if the patients are ranked in ranking order according to their score in the first treatment, and comparison is made with their score in the second, "tau", which should be +1 for complete agreement and −1 for complete disagreement, comes out at 0.25.

Discussion

This trial was planned to explore the possibilities of a cross-over design, and not primarily designed to
evaluate the substances used. Despite the small number of observations, some trends of interest for the design of more definitive trials may be noted. The spacing, amount, and duration of injections seemed to be adequate to produce quite marked changes in some criteria. It must be remembered that the fortnightly assessment was made before each injection, by which time any analgesic effect from a previous injection of procaine would have worn off. The length of time between the two courses of injections seemed to be adequate to show reversion towards the untreated state. The importance of a preliminary period of training as noted previously (Bywaters, Dixon, and Wild, 1950) is shown here by this difference between the first and second period of injections; it would have been an advantage here to have had a preliminary treatment with some other therapeutic substance.

The criteria of assessment group themselves chiefly into three categories:

(1) Those that showed no regular change and are not further considered;
(2) Those that showed improvement in the first period of either drug, and little or none in the second period (walking time and range of movement);
(3) Those that showed the same trend for each drug, in both the first and second course (limitation of extension and joint tenderness).

The last are to be preferred for the evaluation of differences between drugs. It seems probable that the other two criteria (walking time and range of movement) are more susceptible to non-specific encouragement, and depend on the patient's degree of confidence in himself and his physician. Thus, of the nine criteria used, only two appeared from this pilot study to be of potential value. It is important to define the value of these criteria, since one of the reasons why controlled clinical trials are not performed is the fact that assessment is time-consuming and often tedious, even though, as in this instance, the patients are carefully selected and co-operative, and the examining physicians personally interested in the results of the trial.

Summary

The effects of intra-articular injections of hydrocortisone acetate and of procaine was studied in ten patients, as a pilot scheme.

Each patient was given four fortnightly injections of one drug followed by 8 weeks' rest, and four fortnightly injections of the other drug followed by a further 8 weeks' rest. Five patients chosen at random received hydrocortisone first and five others received procaine first. Assessment was made at fortnightly intervals. The only significant difference was that found between the results of the first treatment and those of the second, regardless of which drug was used.

It was found that the criteria of assessment could be grouped into three categories: those that showed no regular change, those that showed improvement in the first course but not the second, and two (joint tenderness and limitation of extension) which showed a similar change for each drug whether the drug was given in the first or in the second course of injections. On these two criteria hydrocortisone acetate appeared to show some slight advantage over procaine, although this was not statistically significant.

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REFERENCES


Étude-pilote d'emploi intra-articulaire de la procaine et de l'acétate d'hydrocortisone dans l'arthrite rhumatismatise

RÉSUMÉ

L'effet d'injections intra-articulaires d'acétate d'hydrocortisone et de procaine fut étudié sur dix malades à titre d'expérience-pilote.

Chaque malade reçoit quatre injections bi-hebdomadaires de l'une des substances, suivies par huit semaines de repos, puis quatre injections bi-hebdomadaires de l'autre substance, suivies à nouveau de huit semaines de repos. Cinq malades, choisis au hasard, furent traités par l'hydrocortisone et cinq autres furent traités d'abord à la procaine. L'évaluation des résultats fut faite à des intervalles bi-hebdomadaires.

La seule différence significative, fut celle observée entre les résultats du premier traitement et ceux du second, quelle que fût la substance employée.

On trouva que les critères d'évaluation des résultats pouvaient être rangés en trois catégories: ceux qui ne montreraient aucun changement constant, ceux qui accusaient une amélioration dans la première partie du traitement mais non dans la seconde et ceux, comprenant la sensibilité articulaire et la limitation de l'extension, qui accusaient un changement similaire pour chaque substance, que celle-ci fût administrée durant la première ou la seconde série d'injections. Selon ces deux critères, l'acétate d'hydrocortisone semblait montrer un léger avantage sur la procaine; cet avantage ne fut pas significatif du point de vue statistique.

Estudio-piloto del empleo intra-articular de la procaina y del acetato de hidrocortisona en la artritis reumatoide

SUMARIO

El efecto de inyecciones intra-articulares de acetato de hidrocortisona y de procaina fue estudiado en diez enfermos a título de estudio-piloto.

Cada enfermo recibió cuatro inyecciones quincenales.
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del producto, seguidas de ocho semanas de reposo, luego cuatro inyecciones quincenales del otro producto, también seguidas de ocho semanas de reposo. Cinco enfermos escogidos al azar empezaron con inyecciones de hidrocoristona y los cinco demás con las de procaina. Cada quincena se evaluaron los resultados.

La única diferencia significativa fue la observada entre los resultados del primer tratamiento y los del segundo, cualquier fuera el producto empleado.

Los criterios de evaluación se podían agrupar en tres categorías: los que no presentaron cambios constantes, los que acusaron una mejora en la primera parte del tratamiento pero no en la segunda y, finalmente, los que mostraron una tendencia similar para ambos productos en ambas series de inyecciones. En este tercer grupo se encuentran la sensibilidad articular y la limitación de la extensión. Estos dos criterios sólo se pueden tomar en cuenta y según ellos el acetato de hidrocoristona parece tener una pequeña ventaja, sin importancia estadística, sobre la procaina.
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