INTRA-ARTICULAR THERAPY IN ARTHRITIS
WITH SPECIAL REFERENCE TO HYDROCORTISONE

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Injection of substances as diverse as iodized oil and lactic acid have been used in the past to suppress arthritic inflammation. Hydrocortisone was first given by intra-articular injection by Thorn (1951), but it was not until Hollander et al. (1951) reported considerable and consistent improvement from injections of hydrocortisone acetate into the affected synovial spaces of arthritic patients that this form of treatment was generally adopted. The encouraging early results were confirmed by Stevenson et al. (1952), Duff et al. (1952) and De Seze et al. (1952). Cortisone, on the other hand, proved to have an inconsistent local anti-rheumatic effect when injected into joints, leading in some cases to local irritation rather than relief. The difference is thought to result from more rapid tissue utilization of hydrocortisone, whilst cortisone has first to be metabolized under as yet undefined conditions.

Technique of Injection

Ordinary aseptic precautions are taken with or without local anaesthesia, depending on the ease of entry into the joint cavity. Detailed descriptions of procedure for injection of the various joints have been described elsewhere (Hollander, 1953). It is extremely important to avoid damage to the articular cartilage which regenerates poorly, and trauma to the joint surfaces may produce changes as serious as those being treated. The knee joint may be entered by a lateral approach, or from the medial side just dorsal to the patella. The ankle is most readily injected by an anteromedial approach, the needle being inserted just above the level of the tip of the medial malleolus. The elbow can be injected by a needle inserted parallel to the ulna and just lateral to the olecranon. The shoulder can be entered by a needle inserted from the anterior aspect just below the tip of the coracid process, the wrist dorsally immediately distal to the dorsal radial tubercle, and the finger joints dorsolaterally. Because of its depth, the hip is the most difficult of the larger joints to aspirate and inject; it can usually be entered either by a lateral approach over the greater trochanter or from its anterior aspect. The dose of hydrocortisone (25 to 50 mg. for large joints, 12.5 to 25 mg. for smaller joints) is injected without force after excess synovial fluid has been aspirated. No appreciable benefit derives from the use of larger doses in most instances.

Ziff et al. (1956) described a Hypospray Jet Injector which could be applied to intra-articular injection of hydrocortisone and dispensed with the use of a needle. Both simple and convenient, it was claimed that two-thirds of joints so treated improved, though about a third of patients complained of transient post-injection pain. An obvious disadvantage is that fluid cannot be aspirated from the joint prior to injection.

The principal indication for intra-articular therapy is the inadequate control of arthritis in one or a few joints. Active involvement of multiple joints contra-indicates such treatment unless the disease can be brought under control in all but a few joints by the application of physical measures, rest, and systemic therapy.

Mode of Action

The mechanism by which hydrocortisone ameliorates arthritic inflammation is obscure. The local effect is more than simple analgesia, because studies of the synovial fluid from rheumatoid joints after the intra-articular injection of hydrocortisone show a fall in the number of neutrophil cells, a decrease in joint temperature and a significant increase in viscosity (Yielding et al., 1956). Harris et al. (1958), using radioactive sodium clearance from a joint as a quantitative measure of the local circulation, showed that this correlated well with the local activity of the disease. After injection of 50 mg. of hydrocortisone acetate a reduction in clearance rate towards normal was observed.

Injected microcrystals of hydrocortisone quickly disappear from the synovial fluid, being absorbed and retained by the synovial lining cells (Hollander et al., 1955). Wilson et al. (1953) found that 85 per cent. of a 50-mg. dose of hydrocortisone
injected into the synovial space disappeared within one hour.

Systemic as well as local effects have been observed after intra-articular injections of hydrocortisone acetate. Young et al. (1954) noted clinical improvement in involved but uninjected joints in 21 per cent. of patients with rheumatoid arthritis. Most of these systemic responses occurred after the injection of 50 mg. or more of hydrocortisone, though a few were seen after injection of 37.5 mg. or less. Oka (1956), by estimation of plasma 17-hydroxycorticosteroid levels, showed that a considerable proportion of hydrocortisone injected into the joints was absorbed into the circulation. Systemic hormonal effects are to be expected if large and frequent doses are given: 100 mg. of hydrocortisone injected into a joint produces an elevation of plasma corticoids comparable to 25 mg. of hydrocortisone by mouth.

Results of Treatment with Intra-Articular Hydrocortisone

The first manifestations of improvement in the treated joint are noted within 12 or 24 hours after injection. Decreased tenderness, swelling, redness and warmth generally follow subjective improvement within a few hours. In a few patients relief occurs within an hour or so and only rarely is it delayed beyond 24 hours.

Most authors report a beneficial response in approximately three-quarters of patients. Hollander et al. (1951), Stevenson et al. (1952) and Kersley and Desmarais (1952) obtained significant improvement in 70 to 80 per cent. of joints treated with intra-articular hydrocortisone acetate and an average duration of improvement of two to three weeks. Hollander (1953) reviewed the results of hydrocortisone acetate injections (average dose, 25 mg.) into the inflamed joints, bursae, or tendon sheaths of 852 patients who shared a total of 8,693 injections. The local result was considered successful in 89 per cent. of 376 patients with rheumatoid arthritis and in 85 per cent. of 289 osteo-arthritis subjects (excluding the hip). In these patients, injections were followed by demonstrable local improvement lasting three days to many weeks, with gradual relapse of the local inflammation to its pre-treatment state. Successive injections were given when symptoms recurred, as many as 47 injections into a single joint. In 296 patients (54 per cent.) the relief was temporary, but repeated injections successfully maintained improvement for more than a year. Young et al. (1954) obtained moderate to marked improvement in 84 per cent. of 148 patients with rheumatoid arthritis, an effect which persisted for two to eight days in the majority. In only seven patients was the procedure without significant benefit. In a small number, remissions of several months occurred but these were probably related to concurrent improvement in the general condition, either spontaneous or induced by other measures of treatment. Forty-eight patients with osteo-arthritis involvement of knee and hip were also treated with good results in 72 per cent. but with a higher proportion of failures (21 per cent.) than occurred in the group with rheumatoid arthritis. Repeated injections were not found to give progressively greater or more prolonged improvement.

The effect of intra-articular hydrocortisone acetate depends to some extent on the joint injected. Results in the knees are generally better than in other joints, presumably because of the ease with which injection can be accomplished. A good response is usually obtained in the small joints of the fingers, the elbow, ankle and wrist. The more difficult a joint is to aspirate and inject, the poorer the result. Hollander (1953) reported 52 per cent. of failures with injections into the hip.

‘Long-acting’ Derivatives of Hydrocortisone

In 1955 a less soluble ester of hydrocortisone, the tertiary butyl acetate (T.B.A.) was developed for intra-articular therapy with the claim that its anti-inflammatory effects were more pronounced and of longer duration. Hollander et al. (1955) found that of 92 patients with rheumatoid arthritis, 62 experienced greater relief and 49 longer benefit from hydrocortisone T.B.A. than from hydrocortisone. Duff (1956) stated that of the different chemical forms of local hydrocortisone the T.B.A. preparation was probably the most effective. Contradictory results were reported by Zuckner et al. (1956) who found no difference in anti-rheumatic response between the two compounds. The average duration of improvement in both rheumatoid arthritis and osteo-arthritis was two to three weeks with each compound. Larger doses of hydrocortisone T.B.A. (100 mg.) enjoyed no consistent superiority over smaller doses (25 mg.) and it was concluded that 25 mg. was the optimum dose even for large joints. Satisfactory improvement from intra-articular therapy was noted in 80 per cent. of patients.

None of these studies were made in strictly controlled conditions. In a double-blind crossover trial, Chandler et al. (1958) evaluated these drugs in 24 patients with rheumatoid arthritis whose main incapacity arose from involvement of the knees. Both compounds showed a significant advantage over placebo. Improvement was generally greater and of longer duration with hydrocortisone T.B.A. than with hydrocortisone, but the difference was not statistically significant.
Prednisone and Prednisolone

Robecchi et al. (1956) obtained disappointing results from intra-articular injections of prednisone. Prednisolone, however, produced marked clinical improvement in doses of 5 to 10 mg. in nine out of ten patients with rheumatoid arthritis, which corresponded quantitatively and qualitatively to the effect of 25 mg. of hydrocortisone acetate. Prednisolone also proved of greater value than prednisone in the local treatment of osteoarthritis of the knee. Robecchi and Vittorio (1957) reported that the trimethyl acetate derivative of prednisolone possessed a therapeutic efficiency superior to all other compounds previously used. Personal experience with these newer compounds suggests that their advantages over hydrocortisone are slight.

Dangers of Intra-Articular Therapy

Hollander (1953) was impressed by the infrequency and almost universally mild character of adverse effects from intra-articular hydrocortisone injections. Of the 8,693 injections given, only 109 (2.3 per cent.) were followed by some untoward reaction, usually a temporary exacerbation of the arthritis. A few patients complained of weakness, either local or general, after injection and four patients developed urticaria at the site of injection. The most serious immediate local complication, septic arthritis, is fortunately rare, but its occasional occurrence demands scrupulous attention to aseptic practice on the part of the operator. Deep-vein thrombosis is sometimes seen in the injected leg but it is difficult to know if this is a true complication of treatment.

A potentially more serious criticism of this form of treatment has been the report of radiological deterioration, sometimes considerable, in the knees of 10 of 18 patients with rheumatoid arthritis who took part in a controlled trial of intra-articular steroid therapy (Chandler and Wright, 1958). The three most useful measurements of joint function (pain, walking time, and range of movement) were considered separately in relation to radiological change. No significant association could be traced between the effects of treatment on pain and range of movement in the two groups of patients with and without radiological progression of arthritis. Improvement in walking time, however, was significantly greater in the group with deterioration. It was concluded that the principal effect of treatment in this group had been the attainment of a standard of performance beyond the capacity of the joint, the very success of treatment carrying with it the threat of accelerating joint destruction. An example of deterioration after intra-articular injections of hydrocortisone is shown in Fig. 1. The same authors (Chandler et al., 1959) have reported...
the production of a virtual Charcot's arthropathy in an osteo-arthritis hip treated over an 18-month period by monthly injections of hydrocortisone. It was considered that the chief cause for radiological progression in these cases was the encouragement of a degree of weight-bearing and mobility which was inherently traumatic.

The implication of these studies is clearly that intra-articular treatment with hydrocortisone should not be allowed more than an adjuvant place in the rehabilitation of the chronic rheumatic patient. Limitation of weight-bearing activities, muscle retraining, and other local and general measures of treatment emphatically remain of first importance. Intra-articular therapy demands particular restraint on the part of the physician, for the symptomatic benefit experienced by the patient may encourage a vicious circle of dependence despite worsening disease. Strict radiological supervision is advisable if prolonged intra-articular administration of hydrocortisone and related compounds is undertaken.

Summary and Conclusions

Undoubtedly intra-articular therapy with hydrocortisone provides a useful additional measure for the treatment of arthritis and generally gives clinical improvement which is encouraging to the physician and appreciated by the patient. It is particularly valuable as an adjunct to the treatment of rheumatoid arthritis in patients with involvement of only a few joints, or in whom general measures of treatment are adequate except in a few joints. In both rheumatoid arthritis and osteoarthritis it is helpful in the management of patients suffering from acute or subacute exacerbations of disease in whom the maximal application of other conservative measures have failed to relieve discomfort. Intra-articular treatment is impracticable in patients with active involvement of multiple joints and also in arthritis of the spinal joints and, to a lesser extent, the hips which respond poorly because of difficulty of access. Best results are obtained in joints which show signs of active inflammatory change. In patients with advanced joint destruction and where deformity and ankylosis have occurred the treatment is of little value.

The most favourable response to intra-articular treatment occurs in self-limited conditions such as traumatic bursitis and in such localized lesions as tenosynovitis and tendinitis. In periarthritis of the shoulder, intra-articular hydrocortisone may be usefully combined with both physiotherapy and manipulation, and such combined treatment appears to hasten recovery.

It cannot be over emphasized that intra-articular injection of hydrocortisone is a purely palliative procedure, and is not a substitute for systemic therapy; nor should its use be allowed to supplant the need for local supportive measures of treatment. Indeed, the deterioration that has been observed in weight-bearing joints treated by frequent injections of hydrocortisone indicates that more rather than less vigilance is required. As in other diseases, so in arthritis, symptomatic measures must never be allowed to obscure the importance of a total therapeutic approach.

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