EFFECT OF CORTISONE AND CERTAIN OTHER STEROIDS ON THE PERIPHERAL VASCULATURE IN ARTHRITIS

BY

A. WOODMANSEY AND J. W. BEATTIE

From the Department of Clinical Medicine, University of Leeds, General Infirmary, Leeds, and Meanwood Park Hospital, Leeds

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The frequent occurrence of a defective peripheral circulation in rheumatoid arthritis has now been well established since the early observations of Pemberton (1923). Moreover, many of the therapeutic measures employed in this and allied conditions result in an increased peripheral blood flow.

After intramuscular injections of adrenocorticotrophic hormone (ACTH) changes in the blood flow in the knee joint and an increase in the temperature of the fingers in cases of rheumatoid arthritis were reported by Janus (1950). Improved vasomotor activity after intravenous infusions of ACTH was shown by Beattie and Woodmansey (1953). Although Horwitz, Sayen, Naide, and Hollander (1951) found increased digital temperatures after intramuscular ACTH therapy, they were unable to demonstrate a similar effect with cortisone. We, however, had observed a positive effect after cortisone both on digital temperatures and on thermal response. Moreover, cortisone had earlier been shown plethysmographically by Hines, Wakim, Roth, and Kierland (1950) to produce an increased blood flow in the forearm and legs in cases of scleroderma, and more recently by Catchpole, Jepson, and Kellgren (1954) to cause increased digital blood flow in cases of rheumatoid arthritis.

We are here reporting our work on cortisone and on certain other steroids, investigated not only because they have been administered to patients suffering from rheumatoid arthritis, but also because vascular effects have been attributed to some of them.

Method

The technique employed in these observations was similar to that already in routine use in this Unit, previously described by Woodmansey (1951) and Beattie and Woodmansey (1953). Briefly, it involved skin temperature measurements at various sites (the volar or plantar surfaces of the terminal segments of thumbs and great

toes, and the forehead) during a preliminary period of at least 30 minutes, followed by further observations on the exposed limbs during the time of immersion of one leg in a hot-water bath maintained at 44° C. The actual temperatures were recorded with the instrument described in the previous papers. These procedures were carried out, under controlled conditions in a room maintained at a temperature of 18.5°-19.5° C., before and after a course of treatment with the steroid.

Skin temperature, according to Cooper, Cross, Greenfield, Hamilton, and Scarborough (1949) mirrors the rate of blood flow up to about 34° C. The thermal response involves the stimulation by returning warmed blood of the vasomotor centre in the hypothalamus, and the integrity of the sympathetic system on the efferent side, the resulting vasodilatation depending on inhibition of vasoconstrictor tone, which latter is more marked in the lower than in the upper limbs.

Results

Altogether 57 patients (56 females and one male) were included in this survey, 43 suffering from rheumatoid arthritis and fourteen from osteoarthritis. They were investigated in five groups, each group receiving one of the following steroids: cortisone, testosterone, deoxycorticosterone acetate (DOCA) with ascorbic acid, progesterone, and oestradiol monobenzoate. Only one patient (suffering from rheumatoid arthritis) received two steroids—DOCA with ascorbic acid and progesterone.

During the period of administration of the steroid, the patients received no other specific therapy and no local treatment of the hands and legs was carried out.

Cortisone.—This was administered to twelve patients (eleven females and one male), of whom ten had rheumatoid arthritis and two had osteoarthritis. Seven patients received oral cortisone—100 mg. on the first day and 75 mg. on the succeeding 5 days. Earlier (1951-52) five patients (four females and one male), all suffering from rheumatoid arthritis, received concentrated courses

Fig. 1.—Two preliminary tests before, and improved response in one great toe after cortisone treatment.

parenterally. Four had four injections 8-hourly of 100 mg. and one had six injections 8-hourly of 100 mg. (Figs 1 and 2).

Testosterone.—Testosterone propionate (Testoviron)

Fig. 3.—No alteration in response in great toe after testosterone.

Fig. 2.—Improved response in great toe after cortisone.

was administered by daily intramuscular injections of 25 mg. to eleven patients of whom seven had rheumatoid arthritis. In this group, four patients had eight injections, three had seven, two had six, one had five, and one had four (Fig. 3).

DOCA and Ascorbic Acid.—Deoxycorticosterone acetate 5 mg. by intramuscular and ascorbic acid 1 g. by intravenous injection were given daily to ten patients, six had rheumatoid arthritis and four osteo-arthritis. Treatment was administered to seven patients for 7 days to one for 8 days, and to two for 9 days (Fig. 4).

Progesterone.—Daily intramuscular injections of progesterone BP 25 mg. (25 I.U.) were given to fifteen patients, eight suffering from rheumatoid arthritis and seven from osteo-arthritis. In this group six patients had seven injections, six had six, one had five, and two had four (Fig. 5).

Oestrogen.—Oestradiol monobenzoate 50,000 I.B.U. as progynon B 5 mg. was given by intramuscular injection on alternate days for four doses to ten patients (Figs 6 and 7).

The test* revealed the state of the vascular tone during the preliminary resting period, the promptness or otherwise of the response in the exposed limbs to the thermal stimulus and the steepness and extent of the induced rise of temperature.

* The graphs show the temperatures of one great toe before and after immersion of the opposite leg in hot water.

Fig. 4.—No alteration in response in great toe after DOCA with ascorbic acid.

A numerical assessment of the result of the thermal response test before and after treatment in each case was attempted, as on previous occasions (Woodmansey, 1951; Beattie and Woodmansey, 1953). The thermal response in the foot is considered to be a better criterion for the test than that in the hand. An index representing the gradient of the curve in degrees centigrade per minute was employed. It was calculated by dividing by the

Fig. 5.—No alteration in response in great toe after progesterone.

time in minutes either the increase in temperature attained from 19°C., *i.e.* room temperature, or if the peak was not reached the temperature rise at the end of thirty minutes' immersion.

A statistical analysis of the results obtained in each group was carried out. The difference in the index before and after treatment was calculated for each patient. The mean difference (*md*), the standard deviation (*s*) and the standard error of the mean difference ($s/\sqrt{n}$) for each steroid group were then obtained. The "t" test $\frac{(md \sqrt{n})}{s}$ based on *n*-1

Fig. 6.—No alteration in response in great toe after oestradiol.

Fig. 7.—Improved response in great toe after oestradiol.

degrees of freedom was applied, giving values of 4.6 for cortisone, 0.06 for testosterone, 1.60 for deoxycorticosterone acetate with ascorbic acid, 1.47 for progesterone, and 1.22 for oestradiol. The only significant result is that which followed cortisone therapy, which is highly significant at the 1 per cent. level.

Discussion

Experimental evidence of the vasodilatating effect of oestrogens and androgens has been brought forward by McGrath (1935), Suzman, Freed, and Prag (1938), Ratschow and Klostermann (1938), and Burckhardt (1946). Clinically, a beneficial effect on peripheral vascular conditions was attributed to oestrogens by Wobker (1940), Walker (1942), and McGrath and Herrmann (1944), though this was denied by White and Smithwick (1941). Good results with androgens were claimed by Edwards, Hamilton, and Duntley (1939), Ernst (1942), and Walker (1942), but Zurrow, Saland, Klein, and Goldman (1942), and Beaser and Massell (1942) were not so optimistic in their views.

These conflicting opinions are understandable in the light of our results with these steroids. Whereas with cortisone every patient responded by showing an improvement in the thermo-vascular regulatory mechanism and status, with the other steroids most of the results were negative, although oestradiol therapy produced improvement in half of the cases.

It is of interest here to consider the effects of treatment by these various steroids in rheumatoid arthritis. Perusal of the literature has shown that where investigations of deoxycorticosterone acetate with ascorbic acid, progesterone, oestradiol or testosterone have been carried out, their therapeutic value was in most cases unproven.

None of our patients receiving steroids other than cortisone experienced any improvement in their rheumatic condition. On the other hand all the cortisone treated patients obtained definite benefit. None of the patients appreciated the nature of the therapy in each case.

In the previous series of experiments (Beattie and Woodmansey, 1953) intravenous infusions of ACTH resulted in an improvement in the thermal response test. In the present series only cortisone produced consistently positive results. Moreover, only these two hormones of those investigated are generally recognized as possessing definite anti-rheumatic activity. Further, of the group of eleven patients receiving DOCA with ascorbic acid, nine subsequently received an intravenous infusion of ACTH and six of these showed an improvement in the thermal response test.

The peripheral vascular effect of cortisone, as previously suggested for ACTH, may be an important factor in the pharmacological action. Horwitz and others (1951) have pointed out that this effect may have resulted from an action either directly on the vessels or on their autonomic control, or indirectly on disease factors that caused excessive vascular tone. The results with the thermal response test with cortisone lend further support to our view that the effect is neurovascular via the thermo-regulatory mechanism.

Summary

The effect on the peripheral vasculature of five different steroids (cortisone, deoxycorticosterone acetate with ascorbic acid, testosterone, progesterone, and oestradiol) has been investigated. Altogether 57 patients (43 rheumatoid arthritis and fourteen osteo-arthritis) were studied in five groups, each group receiving one steroid. Cortisone was the only steroid which consistently produced an improvement in the peripheral vascular status and in the arthritic condition. The peripheral vascular effect may be an important factor in the pharmacological action. It is suggested that this effect of cortisone, like that of ACTH, takes place via the thermo-regulatory mechanism.

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REFERENCES

- Beaser, S. B., and Massell, T. B. (1942). *New Engl. J. Med.*, **227**, 46.
- Beattie, J. W., and Woodmansey, A. (1953). *Annals of the Rheumatic Diseases*, **12**, 43.
- Burckhardt, W. (1946). *Schweiz. med. Wschr.*, **76**, 1147.
- Catchpole, B. N., Jepson, R. P., and Kellgren, J. H. (1954). *Annals of the Rheumatic Diseases*, **13**, 302.
- Cooper, K. E., Cross, K. W., Greenfield, A. D. M., Hamilton, D. McK., and Scarborough, H. (1949). *Clin. Sci.*, **8**, 217.
- Edwards, E. A., Hamilton, J. B., and Duntley, S. Q. (1939). *New Engl. J. Med.*, **220**, 865.
- Ernst, W. (1942). *Wien. klin. Wschr.*, **55**, 131. Abs. (1942). *J. Amer. med. Ass.*, **123**, 1082.
- Hines, E. A., Jr., Wakim, K. G., Roth, G. M., and Kierland, R. (1950). *J. Lab. clin. Med.*, **36**, 834.
- Horwitz, O., Sayen, A., Naide, M., and Hollander, J. L. (1951). *Amer. J. med. Sci.*, **221**, 669.
- Janus, O. (1950). *Brit. med. J.*, **2**, 1244.
- McGrath, E. J. (1935). *J. Amer. med. Ass.*, **105**, 854.
- , and Herrmann, L. G. (1944). *Ann. Surg.*, **120**, 607.
- Pemberton, R. (1923). *Amer. J. med. Sci.*, **166**, 833.
- Ratschow, M., and Klostermann, H. C. (1938). *Z. klin. Med.*, **135**, 198.
- Suzman, M. M., Freed, C. C., and Prag, J. J. (1938). *S. Afr. med. Sci.*, **3**, 29.
- Walker, T. C. (1942). *J. clin. Endocr.*, **2**, 560.
- White, J. C., and Smithwick, R. H. (1941). "The Autonomic Nervous System", 2nd ed. Macmillan, New York.
- Wobker, W. (1940). *Deutsch. med. Wschr.*, **66**, 1265.
- Woodmansey, A. (1951). *Annals of the Rheumatic Diseases*, **10**, 65.
- Zurrow, H., Saland, G., Klein, C., and Goldman, S. (1942). *J. Lab. clin. Med.*, **28**, 269.

Effet de la cortisone et de certains autres stéroïdes sur les vaisseaux périphériques dans l'arthrite

RÉSUMÉ

On étudia l'effet de cinq stéroïdes différents (cortisone, acétate de deoxycorticostérone avec acide ascorbique, testostérone, progestérone et estradiol) sur les vaisseaux périphériques. En tout 57 malades (43 cas d'arthrite rhumatismale et 14 d'ostéoarthritis) furent repartis entre cinq groupes, chaque groupe recevant un des stéroïdes. La cortisone fut le seul stéroïde à produire constamment une amélioration de l'état vasculaire périphérique et de l'arthrite. L'effet vasculaire périphérique peut être un facteur important de l'action pharmacologique. On suggère que cet effet de la cortisone, de même que celui de l'ACTH, s'obtiendrait par l'intermédiaire du mécanisme thermo-régulateur.

El efecto de la cortisona y de ciertos otros esteroides sobre los vasos periféricos en la artritis

SUMARIO

Se estudió el efecto de cinco esteroides diferentes (cortisona, acetato de deoxicorticosterona con ácido ascórbico, testosterona, progesterona y estradiol) sobre los vasos periféricos. Un total de 57 enfermos (43 con artritis reumatoide y 14 con osteoartritis) fué repartido en cinco grupos, cada grupo recibiendo uno de los esteroides. La cortisona fué el único esteroide capaz de causar constantemente una mejoría del estado vascular periférico y de la artritis. El efecto vascular periférico puede constituir un factor importante de la acción farmacológica. Se sugiere que este efecto de la cortisona, así como el de la ACTH, obra por medio del mecanismo termo-regulador.